

*Appendix 1. PRISMA Checklist (attached online)*

**PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis**

Section/Topic	Item #	Checklist Item	Reported on Page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review <i>incorporating a network meta-analysis (or related form of meta-analysis)</i> .	
<b>ABSTRACT</b>			
Structured summary	2	<p>Provide a structured summary including, as applicable:</p> <p><b>Background:</b> main objectives</p> <p><b>Methods:</b> data sources; study eligibility criteria, participants, and interventions; study appraisal; and <i>synthesis methods, such as network meta-analysis</i>.</p> <p><b>Results:</b> number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; <i>treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.</i></p> <p><b>Discussion/Conclusions:</b> limitations; conclusions and implications of findings.</p> <p><b>Other:</b> primary source of funding; systematic review registration number with registry name.</p>	
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known, <i>including mention of why a network meta-analysis has been conducted</i> .	
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
<b>METHODS</b>			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. <i>Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification)</i> .	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable,	

		included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
<b>Geometry of the network</b>	<b>S1</b>	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). <i>Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.</i>
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: <ul style="list-style-type: none"> <li>• <i>Handling of multi-arm trials;</i></li> <li>• <i>Selection of variance structure;</i></li> <li>• <i>Selection of prior distributions in Bayesian analyses; and</i></li> <li>• <i>Assessment of model fit.</i></li> </ul>
<b>Assessment of Inconsistency</b>	<b>S2</b>	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: <ul style="list-style-type: none"> <li>• Sensitivity or subgroup analyses;</li> <li>• Meta-regression analyses;</li> <li>• <i>Alternative formulations of the treatment network; and</i></li> <li>• <i>Use of alternative prior distributions for Bayesian analyses (if applicable).</i></li> </ul>

## RESULTS†

Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
<b>Presentation of network structure</b>	<b>S3</b>	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.
<b>Summary of network geometry</b>	<b>S4</b>	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. <i>Modified approaches may be needed to deal with information from larger networks.</i>
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. <i>In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.</i> If additional summary measures were explored (such as treatment rankings), these should also be presented.
<b>Exploration for inconsistency</b>	<b>S5</b>	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, <i>P</i> values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, <i>alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses</i> , and so forth).

## DISCUSSION

Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). <i>Comment on the validity of the assumptions, such as transitivity and consistency. Comment</i>

		<i>on any concerns regarding network geometry (e.g., avoidance of certain comparisons).</i>
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
<b>FUNDING</b>		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.

PICOS = population, intervention, comparators, outcomes, study design.

\* Text in italics indicateS wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

### **Box. Terminology: Reviews With Networks of Multiple Treatments**

Different terms have been used to identify systematic reviews that incorporate a network of multiple treatment comparisons. A brief overview of common terms follows.

*Indirect treatment comparison:* Comparison of 2 interventions for which studies against a common comparator, such as placebo or a standard treatment, are available (i.e., indirect information). The direct treatment effects of each intervention against the common comparator (i.e., treatment effects from a comparison of interventions made within a study) may be used to estimate an indirect treatment comparison between the 2 interventions (**Appendix Figure 1, A**). An indirect treatment comparison (ITC) may also involve multiple links. For example, in **Appendix Figure 1, B**, treatments B and D may be compared indirectly on the basis of studies encompassing comparisons of B versus C, A versus C, and A versus D.

*Network meta-analysis or mixed treatment comparison:* These terms, which are often used interchangeably, refer to situations involving the simultaneous comparison of 3 or more interventions. Any network of treatments consisting of strictly unclosed loops can be thought of as a series of ITCs (**Appendix Figure 1, A and B**). In mixed treatment comparisons, both direct and indirect information is available to inform the effect size estimates for at least some of the comparisons; visually, this is shown by closed loops in a network graph (**Appendix Figure 1, C**). Closed loops are not required to be present for every comparison under study. "Network meta-analysis" is an inclusive term that incorporates the scenarios of both indirect and mixed treatment comparisons.

*Network geometry evaluation:* The description of characteristics of the network of interventions, which may include use of numerical summary statistics. This does not involve quantitative synthesis to compare treatments. This evaluation describes the current evidence available for the competing interventions to identify gaps and potential bias. Network geometry is described further in **Appendix Box 4**.

### **Appendix Box 1. The Assumption of Transitivity for Network Meta-Analysis**

Methods for indirect treatment comparisons and network meta-analysis enable learning about the relative treatment effects of, for example, treatments A and B through use of studies where these interventions are compared against a common therapy, C.

When planning a network meta-analysis, it is important to assess patient and study characteristics across the studies that compare pairs of treatments. These characteristics are commonly referred to as *effect modifiers* and include traits such as average patient age, gender distribution, disease severity, and a wide range of other plausible features.

For network meta-analysis to produce valid results, it is important that the distribution of effect modifiers is similar, for example, across studies of A versus B and A versus C. This balance increases the plausibility of reliable findings from an indirect comparison of B versus C through the common comparator A. When this balance is present, the assumption of transitivity can be judged to hold.

Authors of network meta-analyses should present systematic (and even tabulated) information regarding patient and study characteristics whenever available. This information helps readers to empirically evaluate the validity of the assumption of transitivity by reviewing the distribution of potential effect modifiers across trials.

## **Appendix Box 2. Differences in Approach to Fitting Network Meta-Analyses**

Network meta-analysis can be performed within either a frequentist or a Bayesian framework. Frequentist and Bayesian approaches to statistics differ in their definitions of probability. Thus far, the majority of published network meta-analyses have used a Bayesian approach.

Bayesian analyses return the posterior probability distribution of all the model parameters given the data and prior beliefs (e.g., from external information) about the values of the parameters. They fully encapsulate the uncertainty in the parameter of interest and thus can make direct probability statements about these parameters (e.g., the probability that one intervention is superior to another).

Frequentist analyses calculate the probability that the observed data would have occurred under their sampling distribution for hypothesized values of the parameters. This approach to parameter estimation is more indirect than the Bayesian approach.

Bayesian methods have been criticized for their perceived complexity and the potential for subjectivity to be introduced by choice of a prior distribution that may affect study findings. Others argue that explicit use of a prior distribution makes transparent how individuals can interpret the same data differently. Despite these challenges, Bayesian methods offer considerable flexibility for statistical modeling. In-depth introductions to Bayesian methods and discussion of these and other issues can be found elsewhere.

### **Appendix Box 3. Network Meta-Analysis and Assessment of Consistency**

Network meta-analysis often involves the combination of direct and indirect evidence. In the simplest case, we wish to compare treatments A and B and have 2 sources of information: direct evidence via studies comparing A versus B, and indirect evidence via groups of studies comparing A and B with a common intervention, C. Together, this evidence forms a closed loop, ABC.

Direct and indirect evidence for a comparison of interventions should be combined only when their findings are similar in magnitude and interpretation. For example, for a comparison of mortality rates between A and B, an odds ratio determined from studies of A versus B should be similar to the odds ratio comparing A versus B estimated indirectly based on studies of A versus C and B versus C. This assumption of comparability of direct and indirect evidence is referred to as *consistency* of treatment effects.

When a treatment network contains a closed loop of interventions, it is possible to examine statistically whether there is agreement between the direct and indirect estimates of intervention effect.

Different methods to evaluate potential differences in relative treatment effects estimated by direct and indirect comparisons are grouped as *local approaches* and *global approaches*. Local approaches (e.g., the Bucher method or the node-splitting method) assess the presence of inconsistency for a particular pairwise comparison in the network, whereas global approaches (e.g., inconsistency models,  $\chi^2$  measure for inconsistency) consider the potential for inconsistency in the network as a whole.

Tests for inconsistency can have limited power to detect a true difference between direct and indirect evidence. When multiple loops are being tested for inconsistency, one or a few may show inconsistency simply by chance. Further discussions of consistency and related concepts are available elsewhere.

Inconsistency in a treatment network can indicate lack of transitivity (see **Appendix Box 1**).

#### **Appendix Box 4. Network Geometry and Considerations for Bias**

The term *network geometry* is used to refer to the architecture of the treatment comparisons that have been made for the condition under study. This includes what treatments are involved in the comparisons in a network, in what abundance they are present, the respective numbers of patients randomly assigned to each treatment, and whether particular treatments and comparisons may have been preferred or avoided.

Networks may take on different shapes. Poorly connected networks depend extensively on indirect comparisons. Meta-analyses of such networks may be less reliable than those from networks where most treatments have been compared against each other.

Qualitative description of network geometry should be provided and accompanied by a network graph. Quantitative metrics assessing features of network geometry, such as *diversity* (related to the number of treatments assessed and the balance of evidence among them), *co-occurrence* (related to whether comparisons between certain treatments are more or less common), and *homophily* (related to the extent of comparisons between treatments in the same class versus competing classes), can also be mentioned.

Although common, established steps for reviewing network geometry do not yet exist, however examples of in-depth evaluations have been described related to treatments for tropical diseases and basal cell carcinoma and may be of interest to readers. An example based on 75 trials of treatments for pulmonary arterial hypertension (**Appendix Figure 3**) suggests that head-to-head studies of active therapies may prove useful to further strengthen confidence in interpretation of summary estimates of treatment comparisons.

## **Appendix Box 5. Probabilities and Rankings in Network Meta-Analysis**

Systematic reviews incorporating network meta-analyses can provide information about the hierarchy of competing interventions in terms of treatment rankings.

The term *treatment ranking probabilities* refers to the probabilities estimated for each treatment in a network of achieving a particular placement in an ordering of treatment effects from best to worst. A network of 10 treatments provides a total of 100 ranking probabilities—that is, for each intervention, the chance of being ranked first, second, third, fourth, fifth, and so forth).

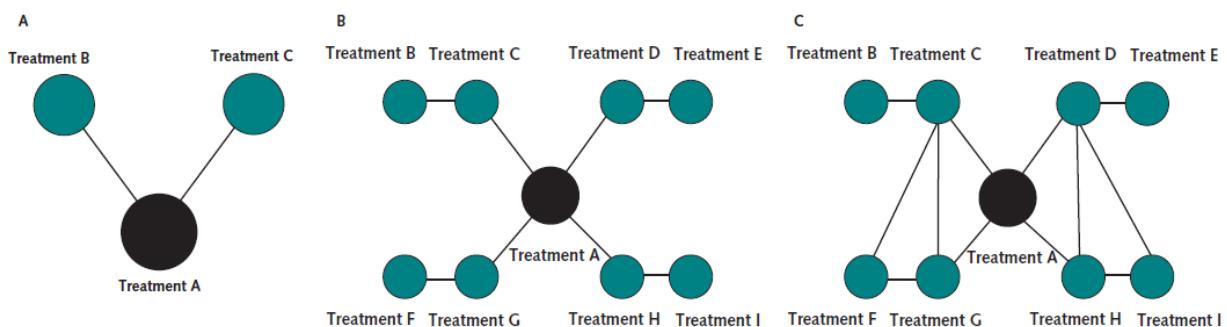
Several techniques are feasible to summarize relative rankings, and include graphical tools as well as different approaches for estimating ranking probabilities. **Appendix Figure 6** shows 2 approaches to presenting such information, on the basis of a comparison of adjuvant interventions for resected pancreatic adenocarcinoma.

Robust reporting of rankings also includes specifying median ranks with uncertainty intervals, cumulative probability curves, and the surface under the cumulative ranking (SUCRA) curve.

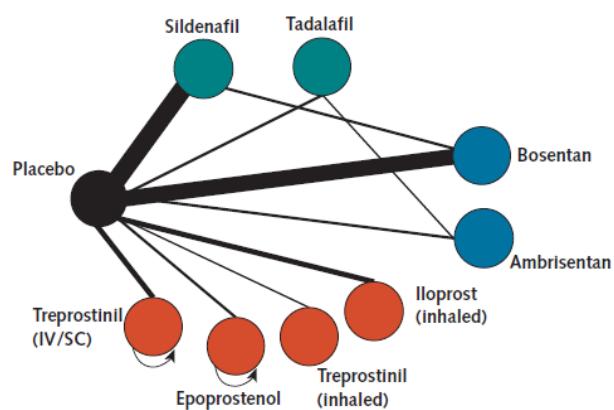
Rankings can be reported along with corresponding estimates of pairwise comparisons between interventions. Rankings should be reported with probability estimates to minimize misinterpretation from focusing too much on the most likely rank.

Rankings may exaggerate small differences in relative effects, especially if they are based on limited information. An objective assessment of the strength of information in the network and the magnitude of absolute benefits should accompany rankings to minimize potential biases.

**Appendix Figure 1A-1C**

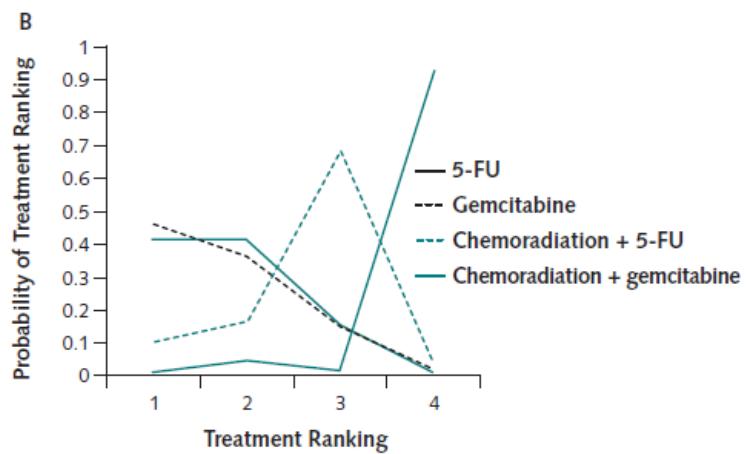


**Appendix Figure 3**



**Appendix Figure 6**

Ranking	Treatment and Corresponding Ranking Probabilities Grade 3 or 4 Hematologic Toxicity			
	5-FU	Gemcitabine	Chemoradiation + 5-FU	Chemoradiation + gemcitabine
1	0.42	0.42	0.15	0.01
2	0.46	0.36	0.15	0.02
3	0.10	0.17	0.68	0.04
4	0.02	0.05	0.02	0.93



## *Appendix 2. Search Strategy*

EMBASE: inception to April 29, 2019

Search step	Hits
1. Exp bipolar depression	5654
2. Exp drug therapy	2582411
3. Exp antidepressant agent	425647
4. Exp neuroleptic agent/ or exp anticonvulsive agent/ or exp lithium/ or exp mood stabilizer/ or exp carbamazepine/ or exp tranquilizer/ or exp valproic acid	715479
5. 2 or 3 or 4	333186
<b>6. 1 and 5</b>	<b>3797</b>

MEDLINE: inception April 29, 2019

Search step	Hits
1. Exp bipolar depression	37,841
2. Exp antidepressant agents	136,837
3. Exp antipsychotic agents	116,433
4. Exp anticonvulsants	132,520
5. Exp lithium	214,64
6. Exp Valproic acid/ or exp antimanic agents	31,021
7. Exp carbamazepine	10,700
8. Ex" "Hypnotics and Sedativ"s"/ or exp anti-anxiety agents/ or exp tranquilizing agents	278,615
9. 2 or 3 or 4 or 5 or 6 or 7 or 8	456,765
10. Exp depression	1011
11. 1 and 10	3058
12. 9 and 11	1011
<b>13. Limit 12 to (English language and humans and randomized controlled trial)</b>	<b>45</b>

PsycINFO: inception to April 29, 2019

Search step	Hits
1. Exp bipolar disorder	25,423
2. Exp major depression	120,470
3. 1 and 2	5,781
4. Ex drug therapy/ or exp neuroleptic drugs/ or exp antidepressant drugs	158,097
5. Exp lithium	6,256
6. Exp anticonvulsive drugs	11,284
7. Exp valproic acid	1,691
8. Exp carbamazepine	1,414
9. Exp sedatives/ or exp tranquilizing drugs/ or exp minor tranquilizers	1,052
10. 4 or 5 or 6 or 7 or 8 or 9	315,321
11. 3 and 10	1,652

**12. Limit 11 to (human and English language an""""300  
clinical tri"l")** 135

Cochrane Library: inception April 29, 2019

Search step	Hits
1. MeSH descriptor: [Bipolar Disorder] explode all trees	23,18
2. MeSH descriptor: [Psychotropic Drugs] explode all trees	12,770
3. MeSH descriptor: [Antidepressive Agents] explode all trees	5,360
4. MeSH descriptor: [Antipsychotic Agents] explode all trees	4,289
5. MeSH descriptor: [Lithium] explode all trees	647
6. MeSH descriptor: [Anticonvulsants] explode all trees	2,268
7. MeSH descriptor: [Valproic Acid] explode all trees	867
8. MeSH descriptor: [Antimanic Agents] explode all trees	386
9. MeSH descriptor: [Hypnotics and Sedatives] explode all trees	3,356
10. 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	18,725
11. MeSH descriptor: [Depressive Disorder, Major] explode all trees	4,044
12. 1 and 11	198
13. 10 and 12	72
<b>14. Limit 13 to (Trials)</b>	<b>72</b>

PubMed: inception to April 29, 2019

Search step	Hits"
1. ("bipolar depressi"n") AND (((((((antidepressants) OR mood stabilizer) OR neuroleptic) OR lithium) OR valpro*) OR anticonvulsant) OR antiepileptic) OR carbamazepine) OR sedative)	1,276
<b>2. Limit to Randomized Controlled Trial</b>	<b>165</b>

CINAHL and Pre-CINAHL: inception to April 29, 2019

Search step	Hits
1. (MH "Bipolar Disorder") OR ""bipolar depression"	10,390
2. (MH "Antidepressive Agents") OR (MH "Antipsychotic Agents") OR "neuroleptic" OR (MH "Lithium") OR "lithium" OR (MH "Lithium Carbonate") OR (MH "Lithium Compounds") OR (MH "Anticonvulsants") OR (MH "Valproic Acid") OR (MH "Topiramate") OR (MH "Tiagabine Hydrochloride") OR (MH "Tiagabine") OR (MH "Primidone") OR (MH "Pregabalin") OR (MH "Phenytoin") OR (MH "Phenobarbital") OR (MH "Lamotrigine") OR (MH "Gabapentin") OR "anticonvulsant" OR "bipolar depression" OR (MH "Antianxiety Agents, Benzodiazepine") OR (MH "Temazepam") OR (MH "Quazepam") OR "benzodiazepines" OR (MH "Drug Therapy") OR "pharmacotherapy"	60,919
3. (MH "Randomized Controlled Trials")	81,466
<b>4. 1 and 2 and 3</b>	<b>101</b>

LILACS: inception to April 29, 2019

Search step	Hit"
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**1. “bipolar depression” and randomized controlled trial 5**

WHO's International Clinical Trials Registry Platform (ICTRP): inception to April 30, 2019	
Search step	Hits
1. URL: <a href="https://www.who.int/ictrp/en/">https://www.who.int/ictrp/en/</a>	
2. List by Health Topics: <a href="http://apps.who.int/trialsearch/ListBy.aspx?TypeListing=0">http://apps.who.int/trialsearch/ListBy.aspx?TypeListing=0</a>	
3. Search “bipolar” and “depression” restricted to “Results available.”	0

US Food and Drug Administration Clinicaltrials.gov Database: inception to April 30, 2019

Search step	Hits
1. URL: <a href="https://clinicaltrials.gov/">https://clinicaltrials.gov/</a>	
2. Advanced search: “Bipolar Disorder Depression” and “Interventional Studies (Clinical Trial)” AND “with results.”	83

*Appendix 3. Meta-analysis code (attached online)*

```

library(readxl)
library(netmeta)
library(WriteXLS)
library(tidyverse)
library(dplyr)

#####
data <- read_excel("~/Documents/Research/Active Projects/BD NMA Adjunctive/BD NMA
Adjuncts.xlsx",
                     sheet = "Modified Analysis")
attach(data)
data <- as.data.frame(data)
attach(data)

#demographics
table(Year)
table(Country)
table(Agents)
table(Class)
length(Class)
table(Subtype)
table(Study[Subtype=="BP-II"])
sum(N)
sum((N_2)[Treatment_2=="Placebo"])
sum(N)-sum((N_2)[Treatment_2=="Placebo"])
summary(Age)
sd(Age)
sum(F1,F2,F3,F4)

#duration
summary(Weeks)

#arms
table(Study[Arms>2])

#quality
table(Overall_ROB)

#####
# Transform data from arm-based format to contrast-based fRRmat
## Outcome: response
p1 <- pairwise(treat = list(Class_1, Class_2, Class_3, Class_4),
               event = list(Responders_1, Responders_2, Responders_3, Responders_4),
               n = list(N_1, N_2, N_3, N_4),
               studlab = Study,
               data = data,
               sm = "RR")

## Outcome: remission
p2 <- pairwise(treat = list(Class_1, Class_2, Class_3, Class_4),
               event = list(Remitters_1, Remitters_2, Remitters_3, Remitters_4),
               n = list(N_1, N_2, N_3, N_4),
               studlab = Study,
               data = data,
               sm = "RR")

## Outcome: completion
p3 <- pairwise(treat = list(Class_1, Class_2, Class_3, Class_4),
               event = list(Completed_1, Completed_2, Completed_3, Completed_4),
               n = list(N_1, N_2, N_3, N_4),
               studlab = Study,
               data = data,
               sm = "RR")

## Outcome: dropouts (all-cause)

```

```

p4 <- pairwise(treat = list(Class_1, Class_2, Class_3, Class_4),
               event = list(Dropouts_1, Dropouts_2, Dropouts_3, Dropouts_4),
               n = list(N_1, N_2, N_3, N_4),
               studlab = Study,
               data = data,
               sm = "RR")

## Outcome: discontinuation due to adverse events
p5 <- pairwise(treat = list(Class_1, Class_2, Class_3, Class_4),
               event = list(AE_1, AE_2, AE_3, AE_4),
               n = list(N_1, N_2, N_3, N_4),
               studlab = Study,
               data = data,
               sm = "RR")

## Outcome: mania
p6 <- pairwise(treat = list(Class_1, Class_2, Class_3, Class_4),
               event = list(Mania_1, Mania_2, Mania_3, Mania_4),
               n = list(N_1, N_2, N_3, N_4),
               studlab = Study,
               data = data,
               sm = "RR")

## Outcome: symptom improvement (difference)
p7 <- pairwise(treat = list(Class_1, Class_2, Class_3, Class_4),
               mean = list(End_1, End_2, End_3, End_4),
               sd = list(End_SD_1, End_SD_2, End_SD_3, End_SD_4),
               n = list(N_1, N_2, N_3, N_4),
               studlab = Study,
               data = data,
               sm = "SMD")

#####
# Conduct random effects network meta-analysis
## Outcome: response
net1 <- netmeta(p1, comb.fixed = FALSE, reference = "Placebo")
print(summary(net1), digits = 2)

## Outcome: remission
net2 <- netmeta(p2, comb.fixed = FALSE, reference = "Placebo")
print(summary(net2), digits = 2)

## Outcome: completion
net3 <- netmeta(p3, comb.fixed = FALSE, reference = "Placebo")
print(summary(net3), digits = 2)

## Outcome: dropouts (all-cause)
net4 <- netmeta(p4, comb.fixed = FALSE, reference = "Placebo")
print(summary(net4), digits = 2)

## Outcome: discontinuation due to adverse events
net5 <- netmeta(p5, comb.fixed = FALSE, reference = "Placebo")
print(summary(net5), digits = 2)

## Outcome: mania
net6 <- netmeta(p6, comb.fixed = FALSE, reference = "Placebo")
print(summary(net6), digits = 2)

## Outcome: symptom improvement (depression)
net7 <- netmeta(p7, comb.fixed = FALSE, reference = "Placebo", tol.multiarm = 1)
print(summary(net7), digits = 2)

#####
# Network graph with default settings
netgraph(net1, offset = 0.02, cex = 0.55) #response
netgraph(net2) #remission

```

```

netgraph(net3) #completion
netgraph(net4) #dropout (all)
netgraph(net5) #dropout (ae)
netgraph(net6) #mania
netgraph(net7) #symptoms

#####
# Network forest plots
forest(net1, ref="Placebo", xlab="RR for response",
       rightcols=c("effect", "ci", "Pscore"), rightlabs="P-Score", leftcols=c("studlab", "k"),
       leftlabs=c("Contrast\nto Placebo", "Direct\nnComparisons"), just.addcols="right",
       sortvar=-TE, smlab = "Random Effects Model", drop.reference.group = TRUE,
       label.left = "Favors placebo", label.right = "Favors drug")

forest(net2, ref="Placebo", xlab="RR for remission",
       rightcols=c("effect", "ci", "Pscore"), rightlabs="P-Score", leftcols=c("studlab", "k"),
       leftlabs=c("Contrast\nto Placebo", "Direct\nnComparisons"), just.addcols="right",
       sortvar=-TE, smlab = "Random Effects Model", drop.reference.group = TRUE,
       label.left = "Favors placebo", label.right = "Favors drug")

forest(net3, ref="Placebo", xlab="RR for completion",
       rightcols=c("effect", "ci", "Pscore"), rightlabs="P-Score", leftcols=c("studlab", "k"),
       leftlabs=c("Contrast\nto Placebo", "Direct\nnComparisons"), just.addcols="right",
       sortvar=-TE, smlab = "Random Effects Model", drop.reference.group = TRUE,
       label.left = "Favors placebo", label.right = "Favors drug")

forest(net4, ref="Placebo", xlab="RR for all drop outs",
       rightcols=c("effect", "ci", "Pscore"), rightlabs="P-Score", leftcols=c("studlab", "k"),
       leftlabs=c("Contrast\nto Placebo", "Direct\nnComparisons"), just.addcols="right",
       sortvar=-Pscore, smlab = "Random Effects Model", drop.reference.group = TRUE,
       label.left = "Favors drug", label.right = "Favors placebo")

forest(net5, reference.group="Placebo", xlab="RR for dropouts due to adverse events",
       rightcols=c("effect", "ci", "Pscore"), rightlabs="P-Score", leftcols=c("studlab", "k"),
       leftlabs=c("Contrast\nto Placebo", "Direct\nnComparisons"), just.addcols="right",
       sortvar=-Pscore, smlab = "Random Effects Model", drop.reference.group = TRUE,
       label.left = "Favors drug", label.right = "Favors placebo")

forest(net6, ref="Placebo", xlab="RR for mania",
       rightcols=c("effect", "ci", "Pscore"), rightlabs="P-Score", leftcols=c("studlab", "k"),
       leftlabs=c("Contrast\nto Placebo", "Direct\nnComparisons"), just.addcols="right",
       sortvar=-Pscore, smlab = "Random Effects Model", drop.reference.group = TRUE,
       label.left = "Favors drug", label.right = "Favors placebo")

forest(net7, ref="Placebo", xlab="SMD for depression severity change",
       rightcols=c("effect", "ci", "Pscore"), rightlabs="P-Score", leftcols=c("studlab", "k"),
       leftlabs=c("Contrast\nto Placebo", "Direct\nnComparisons"), just.addcols="right",
       sortvar=-Pscore, smlab = "Random Effects Model", drop.reference.group = TRUE,
       label.left = "Favors drug", label.right = "Favors placebo")

#####
# decomposition
decomp.design(net1) #response
decomp.design(net2) #remission
decomp.design(net3) #completion
decomp.design(net4) #dropout (all)
decomp.design(net5) #dropout (ae)
decomp.design(net6) #mania
decomp.design(net7) #symptoms

#####
# Funnel plots
funnel(net1, order = net1$trts, linreg = TRUE, digits.pval = 2,
       legend = FALSE, col = "purple", xlab = "RR for response")

funnel(net2, order = net2$trts, linreg = TRUE, digits.pval = 2,

```

```

        legend = FALSE, col = "blue", xlab = "RR for remission")

funnel(net3, order = net3$trts, linreg = TRUE, digits.pval = 2,
       legend = FALSE, col = "red", xlab = "RR for completion")

funnel(net4, order = net4$trts, linreg = TRUE, digits.pval = 2,
       legend = FALSE, col = "green", xlab = "RR for dropouts")

funnel(net5, order = net5$trts, linreg = TRUE, digits.pval = 2,
       legend = FALSE, col = "yellow", xlab = "RR for dropouts due to adverse events")

funnel(net6, order = net6$trts, linreg = TRUE, digits.pval = 2,
       legend = FALSE, col = "orange", xlab = "RR for mania")

funnel(net7, order = net7$trts, linreg = TRUE, digits.pval = 2,
       legend = FALSE, col = "brown", xlab = "SMD for depression symptoms")

#####
# League tables

league1 <- netleague(net1, comb.fixed = FALSE, digits = 2, seq = netrank(net1))
WriteXLS(league1$random, ExcelFileName = "league_response.xls",
         SheetNames = "response", col.names = FALSE)

league2 <- netleague(net2, comb.fixed = FALSE, digits = 2, seq = netrank(net2))
WriteXLS(league2$random, ExcelFileName = "league_remission.xls",
         SheetNames = "remission", col.names = FALSE)

league3 <- netleague(net3, comb.fixed = FALSE, digits = 2, seq = netrank(net3))
WriteXLS(league3$random, ExcelFileName = "league_completion.xls",
         SheetNames = "completion", col.names = FALSE)

league4 <- netleague(net4, comb.fixed = FALSE, digits = 2, seq = netrank(net4))
WriteXLS(league4$random, ExcelFileName = "league_loss.xls",
         SheetNames = "loss", col.names = FALSE)

league5 <- netleague(net5, comb.fixed = FALSE, digits = 2, seq = netrank(net5))
WriteXLS(league5$random, ExcelFileName = "league_ae.xls",
         SheetNames = "ae", col.names = FALSE)

league6 <- netleague(net6, comb.fixed = FALSE, digits = 2, seq = netrank(net6))
WriteXLS(league6$random, ExcelFileName = "league_mania.xls",
         SheetNames = "mania", col.names = FALSE)

league7 <- netleague(net7, comb.fixed = FALSE, digits = 2, seq = netrank(net7))
WriteXLS(league7$random, ExcelFileName = "league_depression_severity.xls",
         SheetNames = "severity", col.names = FALSE)

#####
library(readxl)
library(netmeta)
library(WriteXLS)
library(tidyverse)
library(dplyr)

#####
data <- read_excel("~/Documents/Research/Active Projects/BD NMA Adjunctive/BD NMA
Adjuncts.xlsx",
                  sheet = "Modified Analysis")
attach(data)

table(Subtype)

```

```

#filter: BP-I
data <-
  data %>%
  filter(Subtype == 'BP-I')
attach(data)

#####pairwise
p1 <- pairwise(treat = list(Class_1, Class_2, Class_3, Class_4),
               event = list(Responders_1, Responders_2, Responders_3, Responders_4),
               n = list(N_1, N_2, N_3, N_4),
               studlab = Study,
               data = data,
               sm = "RR")

## Outcome: remission
p2 <- pairwise(treat = list(Class_1, Class_2, Class_3, Class_4),
               event = list(Remitters_1, Remitters_2, Remitters_3, Remitters_4),
               n = list(N_1, N_2, N_3, N_4),
               studlab = Study,
               data = data,
               sm = "RR")

## Outcome: completion
p3 <- pairwise(treat = list(Class_1, Class_2, Class_3, Class_4),
               event = list(Completed_1, Completed_2, Completed_3, Completed_4),
               n = list(N_1, N_2, N_3, N_4),
               studlab = Study,
               data = data,
               sm = "RR")

## Outcome: dropouts (all-cause)
p4 <- pairwise(treat = list(Class_1, Class_2, Class_3, Class_4),
               event = list(Dropouts_1, Dropouts_2, Dropouts_3, Dropouts_4),
               n = list(N_1, N_2, N_3, N_4),
               studlab = Study,
               data = data,
               sm = "RR")

## Outcome: discontinuation due to adverse events
p5 <- pairwise(treat = list(Class_1, Class_2, Class_3, Class_4),
               event = list(AE_1, AE_2, AE_3, AE_4),
               n = list(N_1, N_2, N_3, N_4),
               studlab = Study,
               data = data,
               sm = "RR")

## Outcome: mania
p6 <- pairwise(treat = list(Class_1, Class_2, Class_3, Class_4),
               event = list(Mania_1, Mania_2, Mania_3, Mania_4),
               n = list(N_1, N_2, N_3, N_4),
               studlab = Study,
               data = data,
               sm = "RR")

## Outcome: symptom improvement (difference)
p7 <- pairwise(treat = list(Class_1, Class_2, Class_3, Class_4),
               mean = list(End_1, End_2, End_3, End_4),
               sd = list(End_SD_1, End_SD_2, End_SD_3, End_SD_4),
               n = list(N_1, N_2, N_3, N_4),
               studlab = Study,
               data = data,
               sm = "SMD")

# Conduct random effects network meta-analysis
## Outcome: response
net1 <- netmeta(p1, comb.fixed = FALSE, reference = "Placebo")

```

```

print(summary(net1), digits = 2)

## Outcome: remission
net2 <- netmeta(p2, comb.fixed = FALSE, reference = "Placebo")
print(summary(net2), digits = 2)

## Outcome: completion
net3 <- netmeta(p3, comb.fixed = FALSE, reference = "Placebo")
print(summary(net3), digits = 2)

## Outcome: dropouts (all-cause)
net4 <- netmeta(p4, comb.fixed = FALSE, reference = "Placebo")
print(summary(net4), digits = 2)

## Outcome: discontinuation due to adverse events
net5 <- netmeta(p5, comb.fixed = FALSE, reference = "Placebo")
print(summary(net5), digits = 2)

## Outcome: mania
net6 <- netmeta(p6, comb.fixed = FALSE, reference = "Placebo")
print(summary(net6), digits = 2)

## Outcome: symptom improvement (depression)
net7 <- netmeta(p7, comb.fixed = FALSE, reference = "Placebo", tol.multiarm = 1)
print(summary(net7), digits = 2)

# Network forest plots
forest(net1, ref="Placebo", xlab="RR for response",
       rightcols=c("effect", "ci", "Pscore"), rightlabs="P-Score", leftcols=c("studlab", "k"),
       leftlabs=c("Contrast\nvs Placebo", "Direct\nnComparisons"), just.addcols="right",
       sortvar=-TE, smlab = "Random Effects Model", drop.reference.group = TRUE,
       label.left = "Favors placebo", label.right = "Favors drug")

forest(net2, ref="Placebo", xlab="RR for remission",
       rightcols=c("effect", "ci", "Pscore"), rightlabs="P-Score", leftcols=c("studlab", "k"),
       leftlabs=c("Contrast\nvs Placebo", "Direct\nnComparisons"), just.addcols="right",
       sortvar=-TE, smlab = "Random Effects Model", drop.reference.group = TRUE,
       label.left = "Favors placebo", label.right = "Favors drug")

forest(net3, ref="Placebo", xlab="RR for completion",
       rightcols=c("effect", "ci", "Pscore"), rightlabs="P-Score", leftcols=c("studlab", "k"),
       leftlabs=c("Contrast\nvs Placebo", "Direct\nnComparisons"), just.addcols="right",
       sortvar=-TE, smlab = "Random Effects Model", drop.reference.group = TRUE,
       label.left = "Favors placebo", label.right = "Favors drug")

forest(net4, ref="Placebo", xlab="RR for all drop outs",
       rightcols=c("effect", "ci", "Pscore"), rightlabs="P-Score", leftcols=c("studlab", "k"),
       leftlabs=c("Contrast\nvs Placebo", "Direct\nnComparisons"), just.addcols="right",
       sortvar=-Pscore, smlab = "Random Effects Model", drop.reference.group = TRUE,
       label.left = "Favors drug", label.right = "Favors placebo")

forest(net5, reference.group="Placebo", xlab="RR for dropouts due to adverse events",
       rightcols=c("effect", "ci", "Pscore"), rightlabs="P-Score", leftcols=c("studlab", "k"),
       leftlabs=c("Contrast\nvs Placebo", "Direct\nnComparisons"), just.addcols="right",
       sortvar=-Pscore, smlab = "Random Effects Model", drop.reference.group = TRUE,
       label.left = "Favors drug", label.right = "Favors placebo")

forest(net6, ref="Placebo", xlab="RR for mania",
       rightcols=c("effect", "ci", "Pscore"), rightlabs="P-Score", leftcols=c("studlab", "k"),
       leftlabs=c("Contrast\nvs Placebo", "Direct\nnComparisons"), just.addcols="right",
       sortvar=-Pscore, smlab = "Random Effects Model", drop.reference.group = TRUE,
       label.left = "Favors drug", label.right = "Favors placebo")

forest(net7, ref="Placebo", xlab="SMD for depression severity change",
       rightcols=c("effect", "ci", "Pscore"), rightlabs="P-Score", leftcols=c("studlab", "k"),
       leftlabs=c("Contrast\nvs Placebo", "Direct\nnComparisons"), just.addcols="right",
       sortvar=-Pscore, smlab = "Random Effects Model", drop.reference.group = TRUE,
       label.left = "Favors drug", label.right = "Favors placebo")

```

```

sortvar=-Pscore, smlab = "Random Effects Model", drop.reference.group = TRUE,
label.left = "Favors drug", label.right = "Favors placebo")

#####
library(readxl)
library(netmeta)
library(WriteXLS)
library(tidyverse)
library(dplyr)

#####
data <- read_excel("~/Documents/Research/Active Projects/BD NMA Adjunctive/BD NMA
Adjuncts.xlsx",
                  sheet = "Modified Analysis")
attach(data)

table(MS)

#filter: MS
data <-
  data %>%
  filter(MS == 'Antipsychotic')
attach(data)

#####pairwise
p1 <- pairwise(treat = list(Class_1, Class_2, Class_3, Class_4),
               event = list(Responders_1, Responders_2, Responders_3, Responders_4),
               n = list(N_1, N_2, N_3, N_4),
               studlab = Study,
               data = data,
               sm = "RR")

## Outcome: remission
p2 <- pairwise(treat = list(Class_1, Class_2, Class_3, Class_4),
               event = list(Remitters_1, Remitters_2, Remitters_3, Remitters_4),
               n = list(N_1, N_2, N_3, N_4),
               studlab = Study,
               data = data,
               sm = "RR")

## Outcome: completion
p3 <- pairwise(treat = list(Class_1, Class_2, Class_3, Class_4),
               event = list(Completed_1, Completed_2, Completed_3, Completed_4),
               n = list(N_1, N_2, N_3, N_4),
               studlab = Study,
               data = data,
               sm = "RR")

## Outcome: dropouts (all-cause)
p4 <- pairwise(treat = list(Class_1, Class_2, Class_3, Class_4),
               event = list(Dropouts_1, Dropouts_2, Dropouts_3, Dropouts_4),
               n = list(N_1, N_2, N_3, N_4),
               studlab = Study,
               data = data,
               sm = "RR")

## Outcome: discontinuation due to adverse events
p5 <- pairwise(treat = list(Class_1, Class_2, Class_3, Class_4),
               event = list(AE_1, AE_2, AE_3, AE_4),
               n = list(N_1, N_2, N_3, N_4),
               studlab = Study,
               data = data,
               sm = "RR")

```

```

## Outcome: mania
p6 <- pairwise(treat = list(Class_1, Class_2, Class_3, Class_4),
               event = list(Mania_1, Mania_2, Mania_3, Mania_4),
               n = list(N_1, N_2, N_3, N_4),
               studlab = Study,
               data = data,
               sm = "RR")

## Outcome: symptom improvement (difference)
p7 <- pairwise(treat = list(Class_1, Class_2, Class_3, Class_4),
               mean = list(End_1, End_2, End_3, End_4),
               sd = list(End_SD_1, End_SD_2, End_SD_3, End_SD_4),
               n = list(N_1, N_2, N_3, N_4),
               studlab = Study,
               data = data,
               sm = "SMD")

# Conduct random effects network meta-analysis
## Outcome: response
net1 <- netmeta(p1, comb.fixed = FALSE, reference = "Placebo")
print(summary(net1), digits = 2)

## Outcome: remission
net2 <- netmeta(p2, comb.fixed = FALSE, reference = "Placebo")
print(summary(net2), digits = 2)

## Outcome: completion
net3 <- netmeta(p3, comb.fixed = FALSE, reference = "Placebo")
print(summary(net3), digits = 2)

## Outcome: dropouts (all-cause)
net4 <- netmeta(p4, comb.fixed = FALSE, reference = "Placebo")
print(summary(net4), digits = 2)

## Outcome: discontinuation due to adverse events
net5 <- netmeta(p5, comb.fixed = FALSE, reference = "Placebo")
print(summary(net5), digits = 2)

## Outcome: mania
net6 <- netmeta(p6, comb.fixed = FALSE, reference = "Placebo")
print(summary(net6), digits = 2)

## Outcome: symptom improvement (depression)
net7 <- netmeta(p7, comb.fixed = FALSE, reference = "Placebo", tol.multiarm = 1)
print(summary(net7), digits = 2)

# Network forest plots
forest(net1, ref="Placebo", xlab="RR for response",
       rightcols=c("effect", "ci", "Pscore"), rightlabs="P-Score", leftcols=c("studlab", "k"),
       leftlabs=c("Contrast\nvs Placebo", "Direct\nnComparisons"), just.addcols="right",
       sortvar=-TE, smlab = "Random Effects Model", drop.reference.group = TRUE,
       label.left = "Favors placebo", label.right = "Favors drug")

forest(net2, ref="Placebo", xlab="RR for remission",
       rightcols=c("effect", "ci", "Pscore"), rightlabs="P-Score", leftcols=c("studlab", "k"),
       leftlabs=c("Contrast\nvs Placebo", "Direct\nnComparisons"), just.addcols="right",
       sortvar=-TE, smlab = "Random Effects Model", drop.reference.group = TRUE,
       label.left = "Favors placebo", label.right = "Favors drug")

forest(net3, ref="Placebo", xlab="RR for completion",
       rightcols=c("effect", "ci", "Pscore"), rightlabs="P-Score", leftcols=c("studlab", "k"),
       leftlabs=c("Contrast\nvs Placebo", "Direct\nnComparisons"), just.addcols="right",
       sortvar=-TE, smlab = "Random Effects Model", drop.reference.group = TRUE,
       label.left = "Favors placebo", label.right = "Favors drug")

```

```

forest(net4, ref="Placebo", xlab="RR for all drop outs",
       rightcols=c("effect", "ci", "Pscore"), rightlabs="P-Score", leftcols=c("studlab", "k"),
       leftlabs=c("Contrast\nto Placebo", "Direct\nnComparisons"), just.addcols="right",
       sortvar=-Pscore, smlab = "Random Effects Model", drop.reference.group = TRUE,
       label.left = "Favors drug", label.right = "Favors placebo")

forest(net5, reference.group="Placebo", xlab="RR for dropouts due to adverse events",
       rightcols=c("effect", "ci", "Pscore"), rightlabs="P-Score", leftcols=c("studlab", "k"),
       leftlabs=c("Contrast\nto Placebo", "Direct\nnComparisons"), just.addcols="right",
       sortvar=-Pscore, smlab = "Random Effects Model", drop.reference.group = TRUE,
       label.left = "Favors drug", label.right = "Favors placebo")

forest(net6, ref="Placebo", xlab="RR for mania",
       rightcols=c("effect", "ci", "Pscore"), rightlabs="P-Score", leftcols=c("studlab", "k"),
       leftlabs=c("Contrast\nto Placebo", "Direct\nnComparisons"), just.addcols="right",
       sortvar=-Pscore, smlab = "Random Effects Model", drop.reference.group = TRUE,
       label.left = "Favors drug", label.right = "Favors placebo")

forest(net7, ref="Placebo", xlab="SMD for depression severity change",
       rightcols=c("effect", "ci", "Pscore"), rightlabs="P-Score", leftcols=c("studlab", "k"),
       leftlabs=c("Contrast\nto Placebo", "Direct\nnComparisons"), just.addcols="right",
       sortvar=-Pscore, smlab = "Random Effects Model", drop.reference.group = TRUE,
       label.left = "Favors drug", label.right = "Favors placebo")

```

*Appendix 4. References to included and excluded studies (attached online)*

References for Included Studies: n=70<sup>1–70</sup>

References for Excluded Studies: n=118

Reason	Number	Citation
Monotherapy	47	71–112
Review article	30	113–142
Secondary analysis	17	143–159
Single-arm, open-label trial	13	160–172
Maintenance treatment	4	173–176
Inappropriate outcomes	5	177–181
Mixed states	2	182,183
Not in English language	2	184,185
Unipolar depression	2	186,187
Inappropriate intervention	1	188

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## Appendix 5. Overview of treatments

TREATMENT	NUMBER OF STUDIES	POOLED SAMPLE SIZE
<b>ANTIDEPRESSANTS</b>		
<i>Agomelatine</i>	1	172
<i>Amitriptyline</i>	2	37
<i>Bupropion</i>	5	133
<i>Citalopram</i>	2	70
<i>Desipramine</i>	1	7
<i>Fluoxetine</i>	6	529
<i>Imipramine</i>	5	213
<i>Moclobemide</i>	1	81
<i>Paroxetine</i>	7	145
<i>Sertraline</i>	2	116
<i>Tranylcypromine</i>	1	8
<i>Venlafaxine</i>	3	160
<b>ANTIPSYCHOTICS</b>		
<i>Aripiprazole</i>	1	11
<i>L-Sulpride</i>	1	15
<i>Lurasidone</i>	2	359
<i>Quetiapine (extended release)</i>	1	50
<i>Risperidone</i>	4	62
<i>Ziprasidone</i>	1	145
<b>MOOD STABILIZERS</b>		
<i>Lamotrigine</i>	7	433
<i>Levetiracetam</i>	1	17
<i>Lithium</i>	1	16
<i>Topiramate</i>	1	18
<b>STIMULANTS</b>		
<i>Armodafinil</i>	5	862
<i>Lisdexamphetamine</i>	1	11
<b>OTHER</b>		
<i>Aspirin</i>	6	72
<i>Celecoxib</i>	2	47
<i>Coenzyme Q10</i>	1	36
<i>Combination nutraceutical</i>	2	122

<i>Creatine</i>	1	9
<i>Infliximab</i>	1	28
<i>Inositol</i>	4	67
<i>L-thyroxine</i>	2	41
<i>Minocycline</i>	3	57
<i>N-acetylcysteine</i>	7	192
<i>Omega 3 Fatty Acids</i>	4	132
<i>Pindolol</i>	2	45
<i>Pioglitazone</i>	2	40
<i>Pramipexole</i>	2	22
<i>Pregnenolone</i>	1	38
<i>S-adenosyl-methionine</i>	1	9
<i>Triiodothyronine</i>	1	11
<i>Vitamin D</i>	1	16

*NMDA RECEPTOR ANTAGONIST*

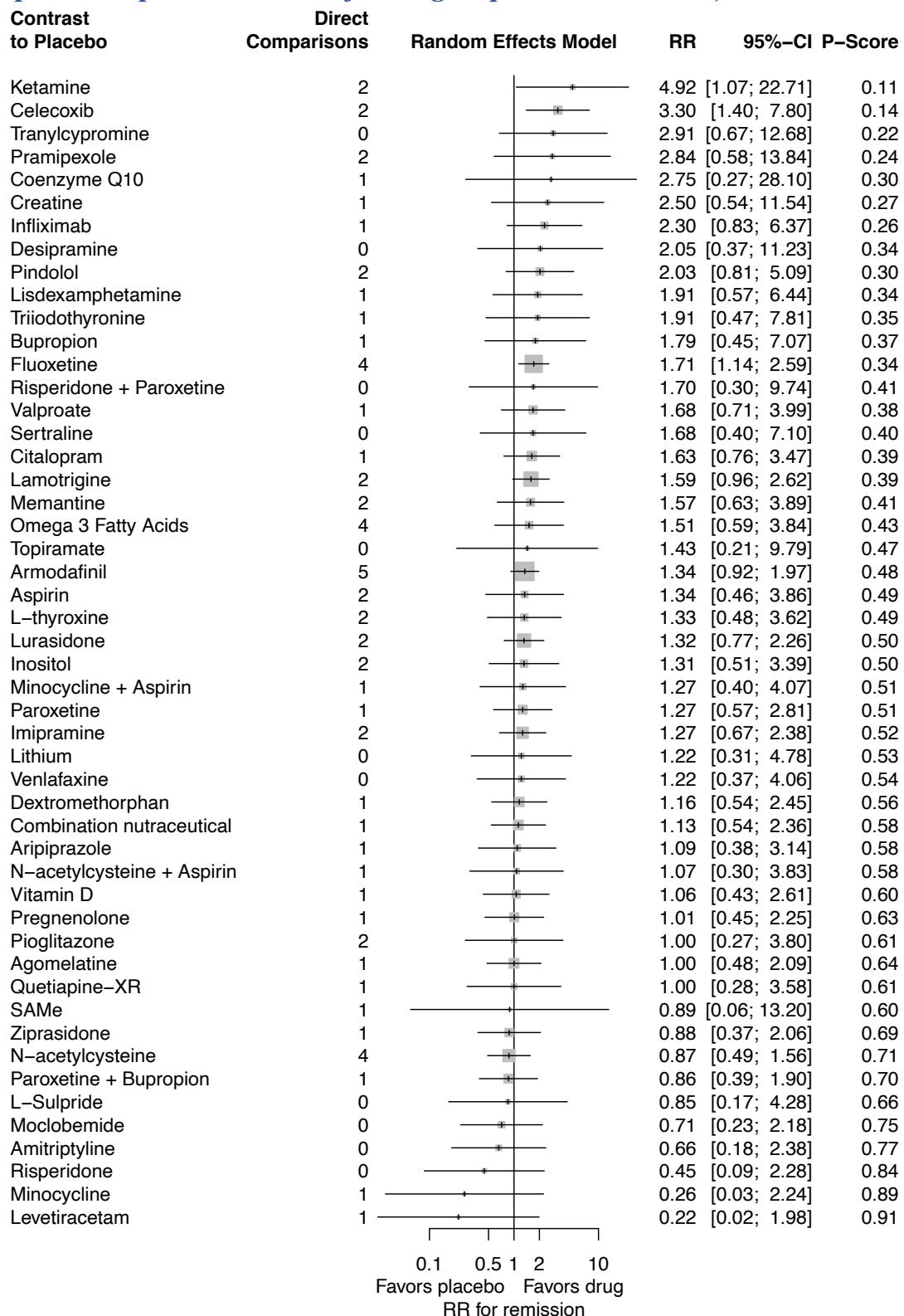
<i>Dextromethorphan</i>	1	203
<i>Racemic intravenous ketamine</i>	2	33
<i>Memantine</i>	2	129

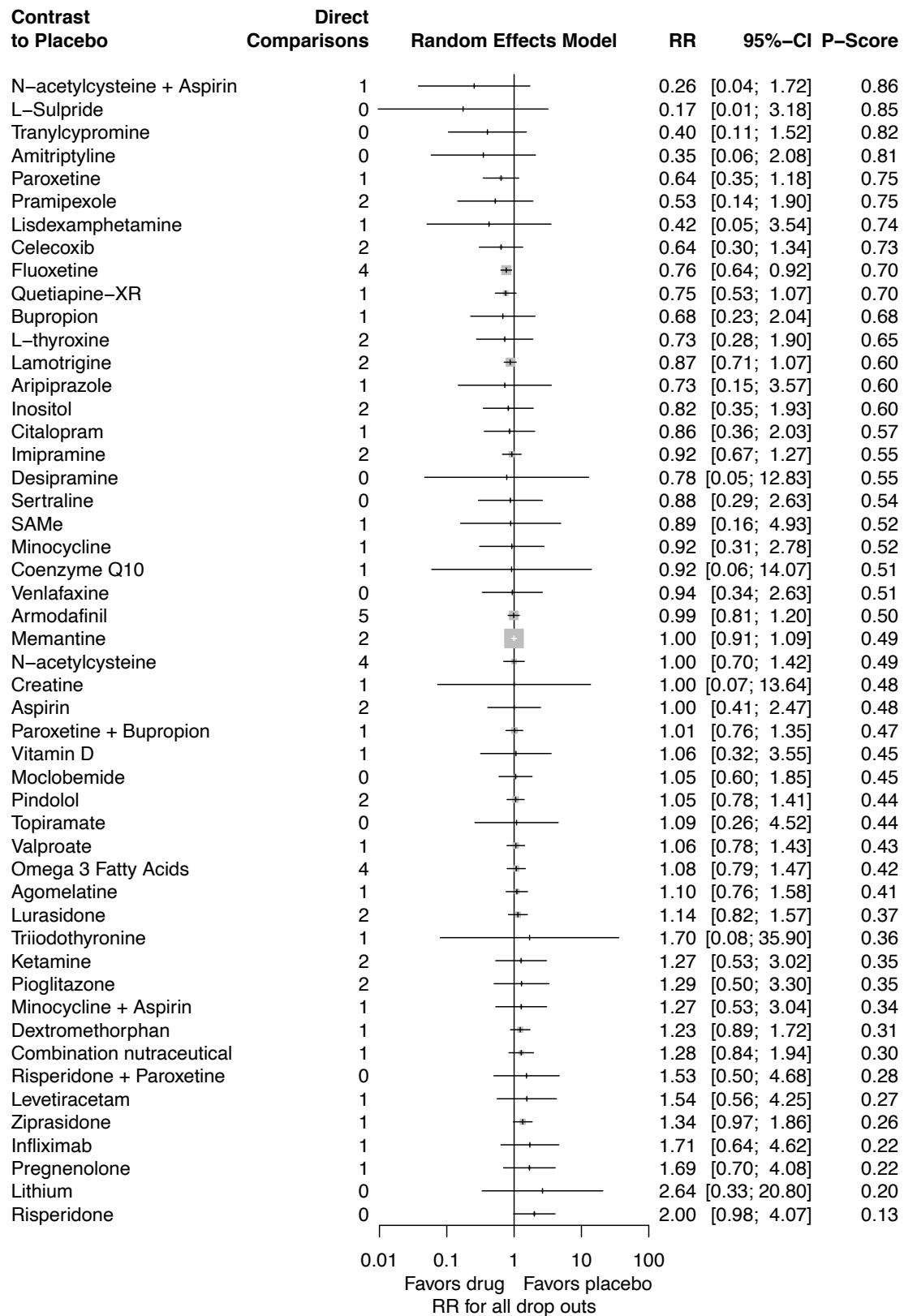
**Appendix 6. Risk of bias graph: review authors' assessments about each risk of bias item presented across all included studies.**

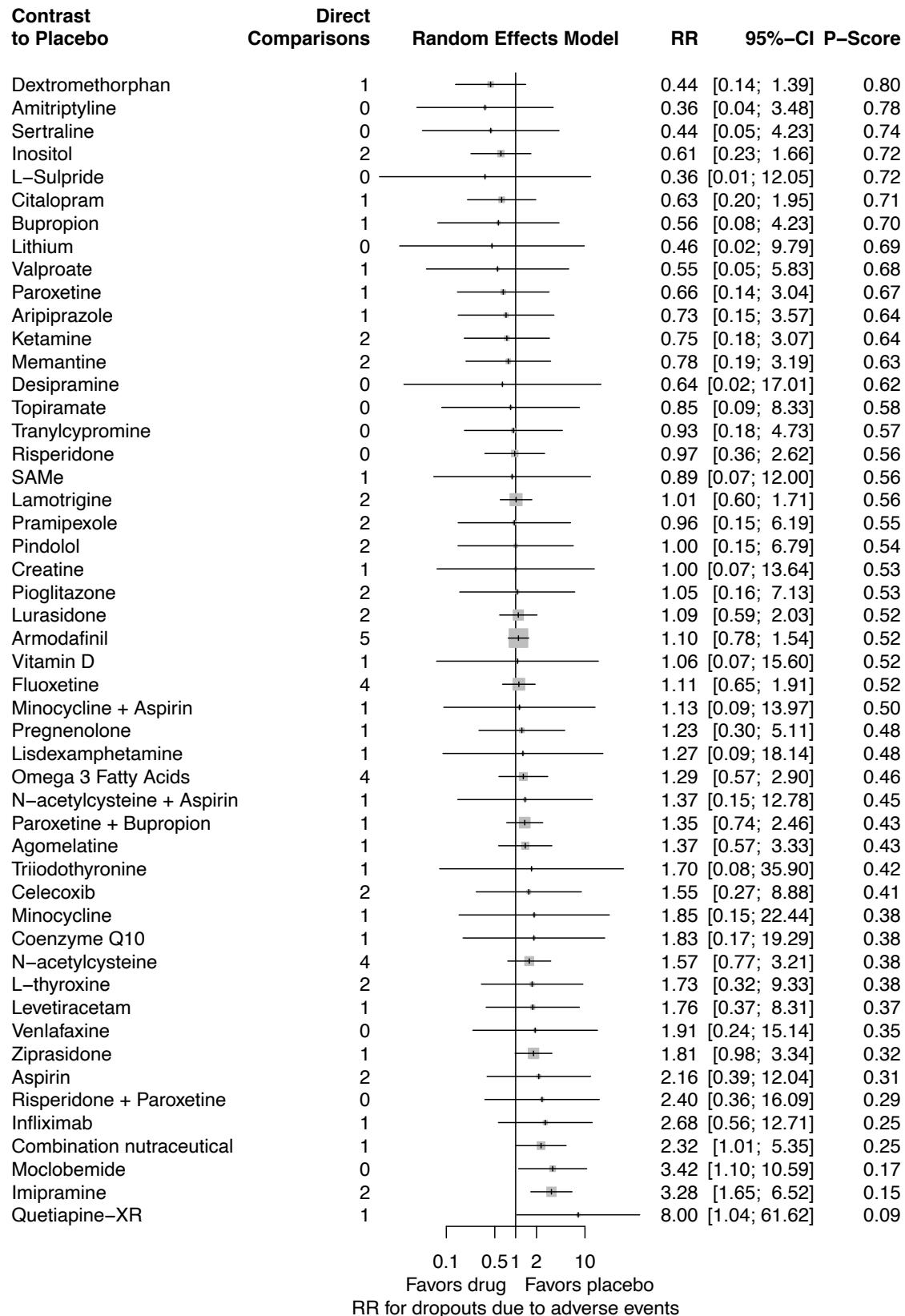
Study	Randomization	Allocation	Blinding (assessors)	Blinding (participants)	Attrition	Selective Reporting	Other Bias	Overall
<i>Aftab 2019</i>	Low	High	Low	Low	Low	Low	Low	Moderate
<i>Amsterdam 2005</i>	Low	High	Low	Low	Low	High	High	High
<i>Anand 2012</i>	Low	Low	Low	Low	Low	Low	Low	Low
<i>Banki 1977</i>	Low	High	Low	Low	Low	Low	High	Moderate
<i>Bauer 1999</i>	Low	High	Low	Low	Low	Low	High	Moderate
<i>Bauer 2018</i>	Low	Low	Low	Low	Low	Low	Low	Low
<i>Berk 2019</i>	Low	High	Low	Low	High	High	Low	High
<i>Bocchetta 1993</i>	Low	Low	Low	Low	Low	Low	Low	Low
<i>Brennan 2013</i>	Low	Low	Low	Low	Low	Low	High	Moderate
<i>Brown 2006</i>	Low	Low	High	High	Low	Low	Low	Moderate
<i>Brown 2014</i>	Low	Low	High	Low	Low	Low	Low	Moderate
<i>Calabrese 2010</i>	Low	Low	Low	Low	Low	Low	High	Moderate
<i>Calabrese 2014</i>	Low	Low	Low	Low	Low	Low	High	Moderate
<i>Chen 2014</i>	Low	Low	Low	Low	Low	Low	High	Moderate
<i>Chengappa 2000</i>	Low	Low	Low	High	Low	Low	Low	Moderate
<i>Cohn 1989</i>	Low	Low	Low	Low	Low	Low	High	Moderate
<i>Detke 2015</i>	Low	Low	Low	Low	Low	Low	High	Moderate
<i>Diazgranados 2010</i>	Low	Low	Low	Low	Low	Low	High	Moderate
<i>Ellegaard 2019</i>	Low	Low	Low	Low	Low	Low	Low	Low
<i>Evins 2006</i>	Low	High	Low	Low	Low	Low	High	Moderate
<i>Frangou 2006</i>	Low	Low	Low	Low	Low	Low	Low	Low
<i>Frye 2007</i>	Low	High	Low	Low	Low	Low	Low	Moderate
<i>Frye 2015</i>	Low	Low	Low	Low	Low	Low	High	Moderate
<i>Gao 2014</i>	Low	High	Low	Low	Low	Low	Low	Moderate
<i>Geddes 2016</i>	High	High	High	Low	Low	Low	Low	High
<i>Geretsegger 2008</i>	Low	Low	Low	Low	Low	Low	High	Moderate
<i>Ghaemi 2015</i>	High	High	Low	Low	Low	Low	Low	Moderate
<i>Goldberg 2004</i>	Low	Low	Low	Low	Low	Low	High	Moderate
<i>Halaris 2020</i>	Low	Low	Low	Low	Low	Low	High	Moderate
<i>Keck 2006</i>	Low	High	Low	Low	Low	Low	High	Moderate
<i>Ketter 2015</i>	Low	Low	Low	High	Low	Low	High	Moderate
<i>Lee 2014</i>	Low	Low	Low	Low	Low	Low	High	Moderate
<i>Loebel 2014</i>	Low	Low	Low	Low	Low	Low	High	Moderate

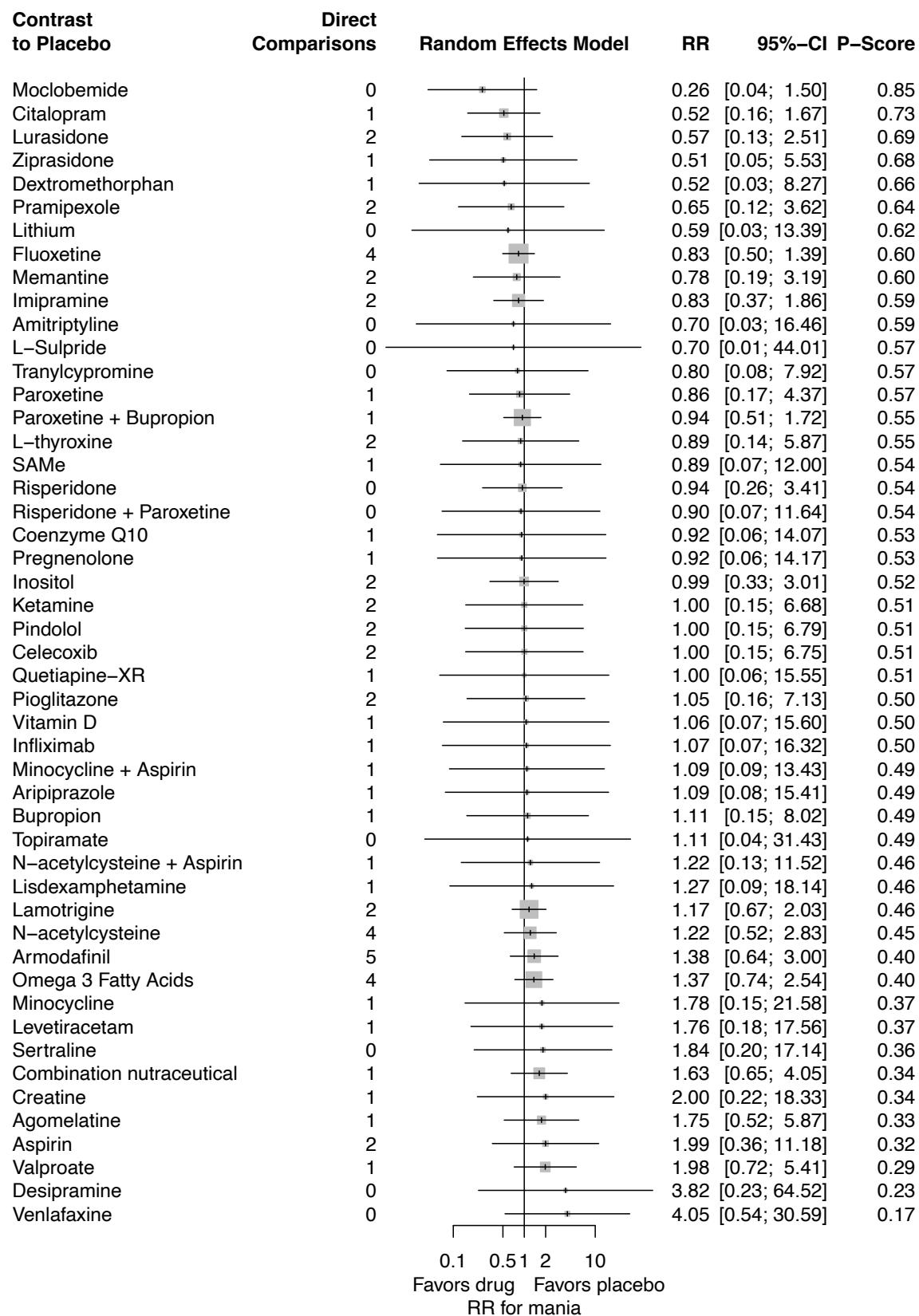


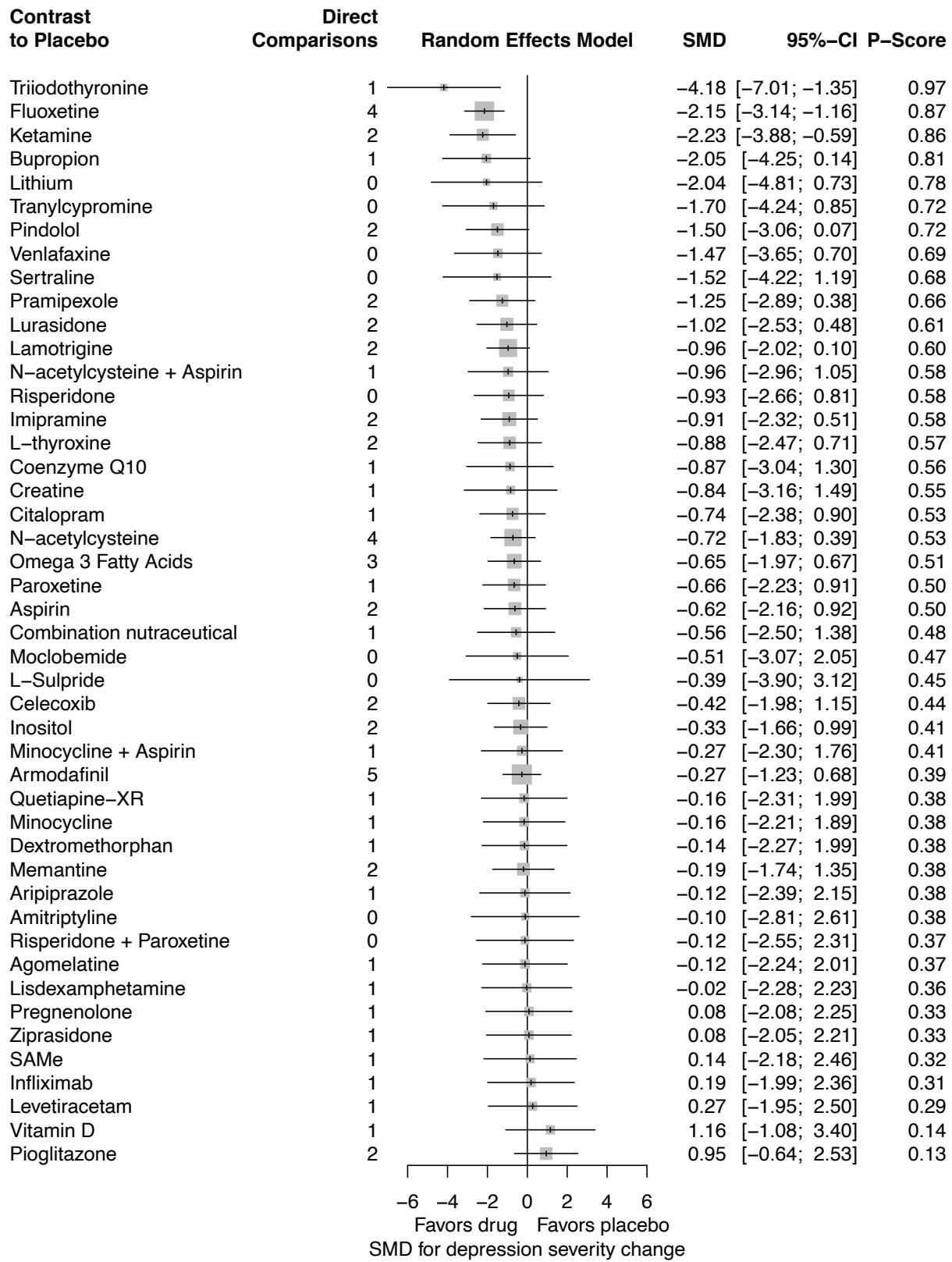
**Appendix 7. Additional contrast plots from network meta-analyses (for all comparisons, placebo is the referent group; RR = rate ratio)**











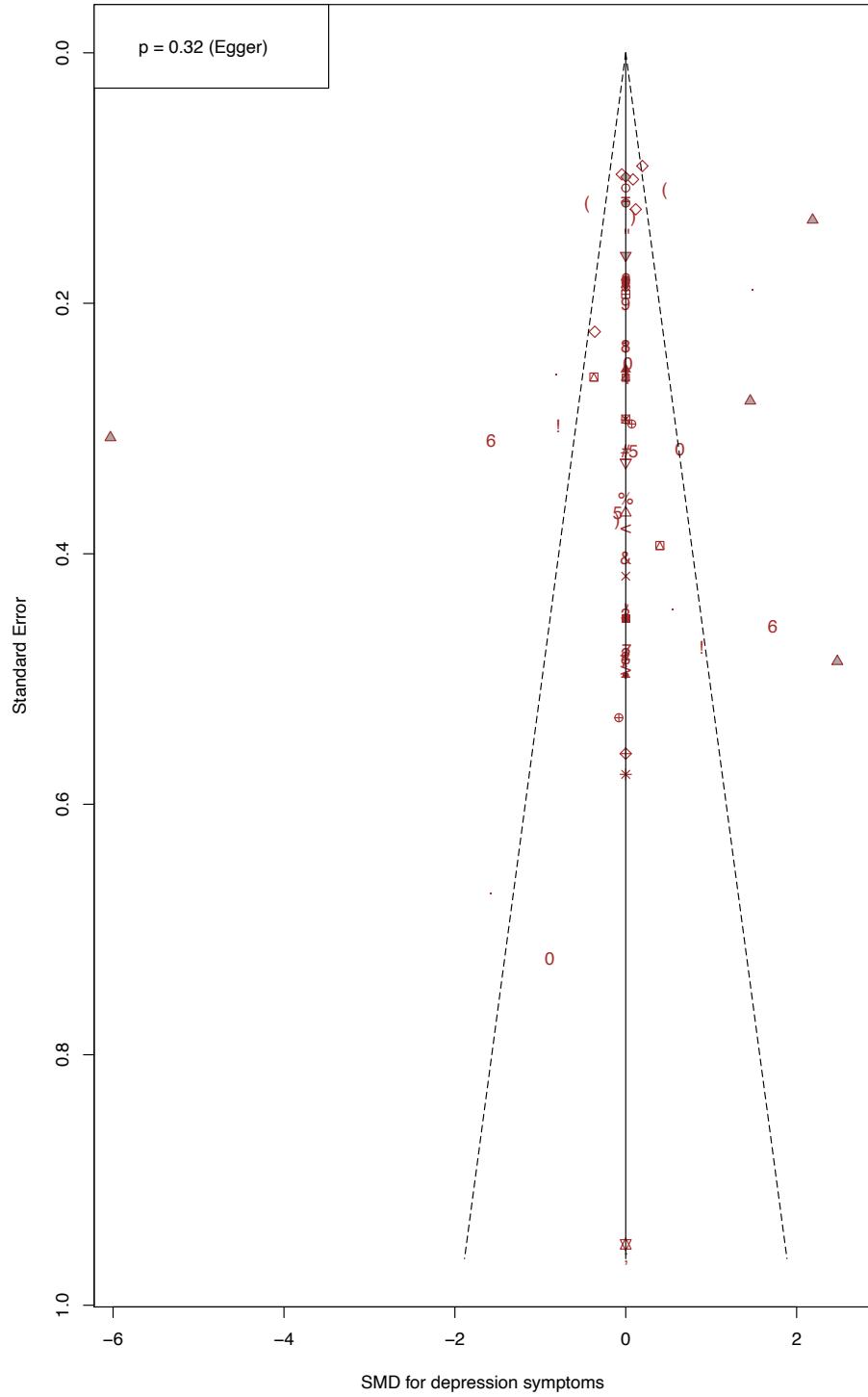
## Appendix 8. Summary of Results

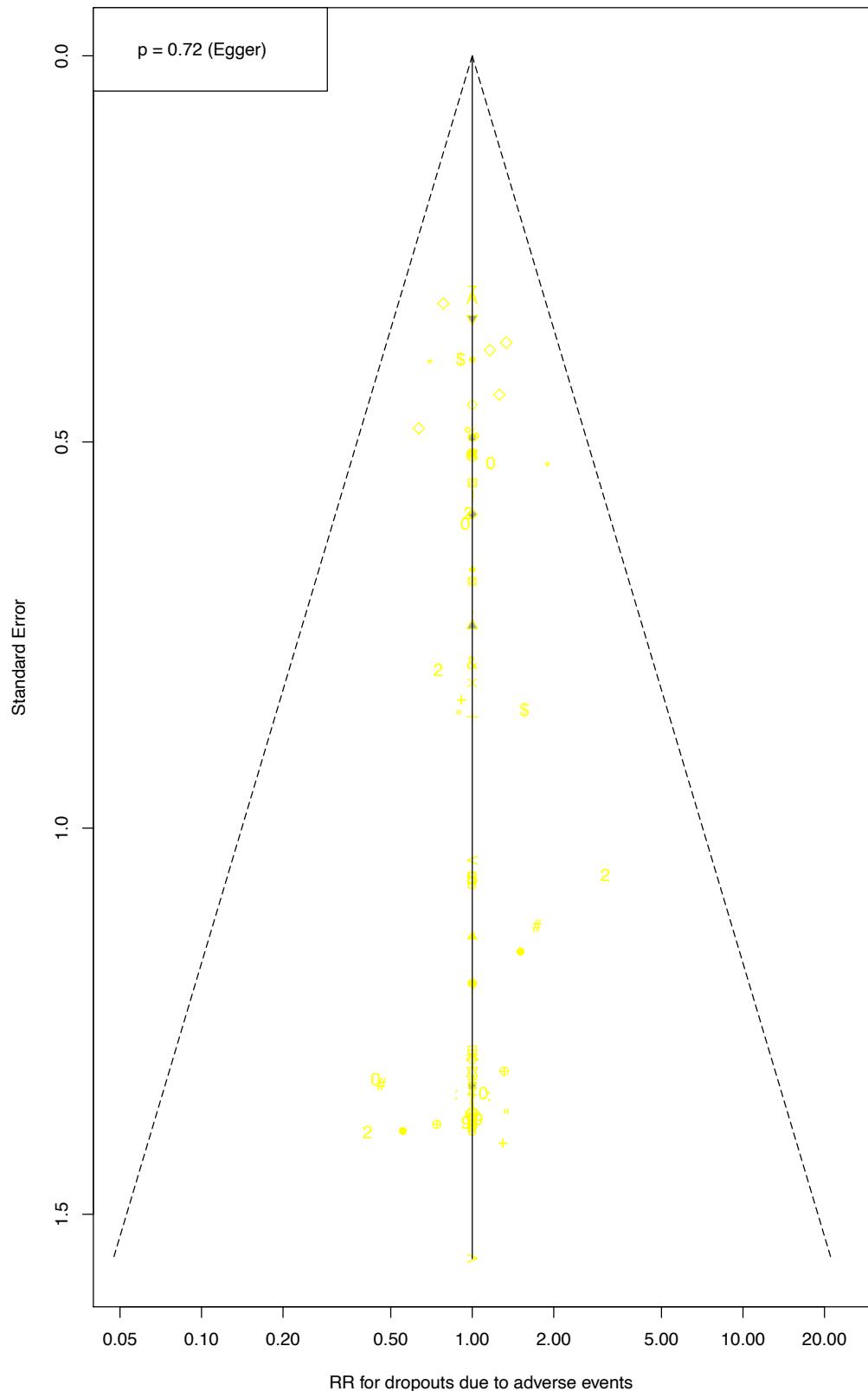
	Significant Findings	$\tau^2$	$I^2$	$Q$ (within)	$p$ (within)	$Q$ (between)	$p$ (between)
Response (RR)	Ketamine: 12.49 (3.06-50.93) CoQ10: 5.96 (2.03-17.48) Pramipexole: 4.17 (1.32-13.18) Fluoxetine: 1.51 (1.11-2.06) Lamotrigine: 1.43 (1.00-2.04)	0.0711	56.3%	31.92	0.0441	36.75	< 0.0001
Completion of Treatment (RR)	Fluoxetine: 1.13 (1.02-1.24) <b>Risperidone: 0.59 (0.38-0.94)</b>	0	0	13.15	0.8707	6.83	0.7411
Remission (RR)	Ketamine: 4.92 (1.07-22.71) Celecoxib: 3.30 (1.40-7.80) Fluoxetine: 1.71 (1.14-2.59)	0.1310	54.1%	25.42	0.1859	39.99	< 0.0001
Reduction in Depression Severity (SMD)	Triiodothyronine: -4.18 (-7.01, -1.35) Fluoxetine: -2.15 (-3.14, -1.16) Ketamine: -2.23 (-3.88, -0.59)	1.1620	96.5%	723.31	< 0.0001	96.54	< 0.0001
All-cause treatment discontinuation (RR)	Fluoxetine: 0.76 (0.64-0.92)	0	0	8.76	0.9853	5.18	0.8792
Discontinuation due to adverse events (RR)	<b>CN: 2.32 (1.01-5.35)</b> <b>Moclobemide: 3.42 (1.10-10.59)</b> <b>Imipramine: 3.28 (1.65-6.52)</b> <b>Quetiapine XR: 8.00 (1.04-61.62)</b>	0	0	15.08	0.7721	4.45	0.9247
Treatment-emergent mood switches (RR)	None	0	0	9.86	0.9707	2.20	0.9946

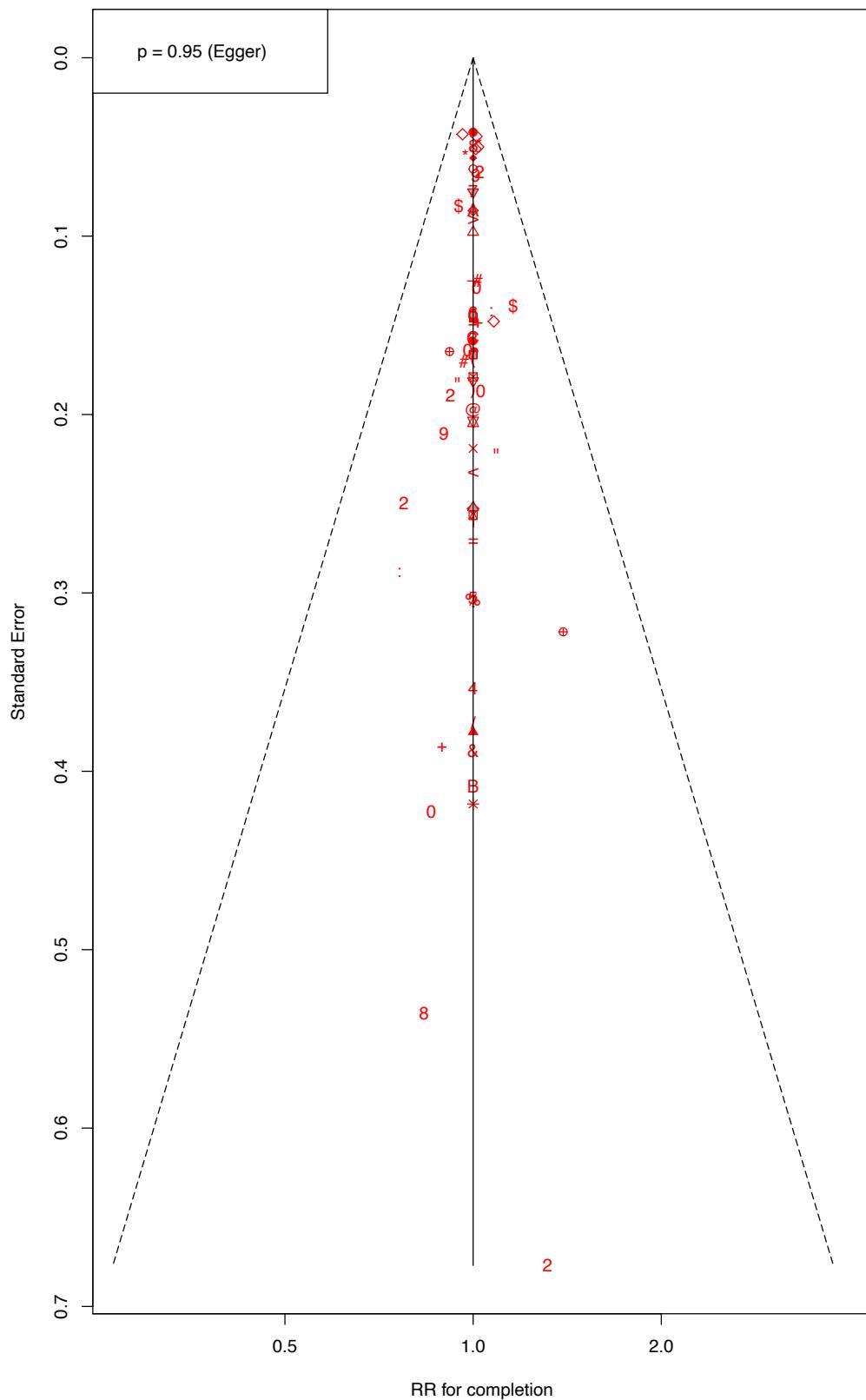
- Black text: agent performed superiorly relative to placebo (e.g., RR >1 for response, remission, acceptability of treatment, etc.)
- Red text: agent performed significantly worse than placebo (e.g., RR <1 for completion of treatment)
- CoQ10: coenzyme Q10
- XR: extended release
- CN: Combination Nutraceutical
- $\tau^2$ ,  $I^2$ , and  $Q$ : measures of between study heterogeneity (greater indicates more heterogeneity)

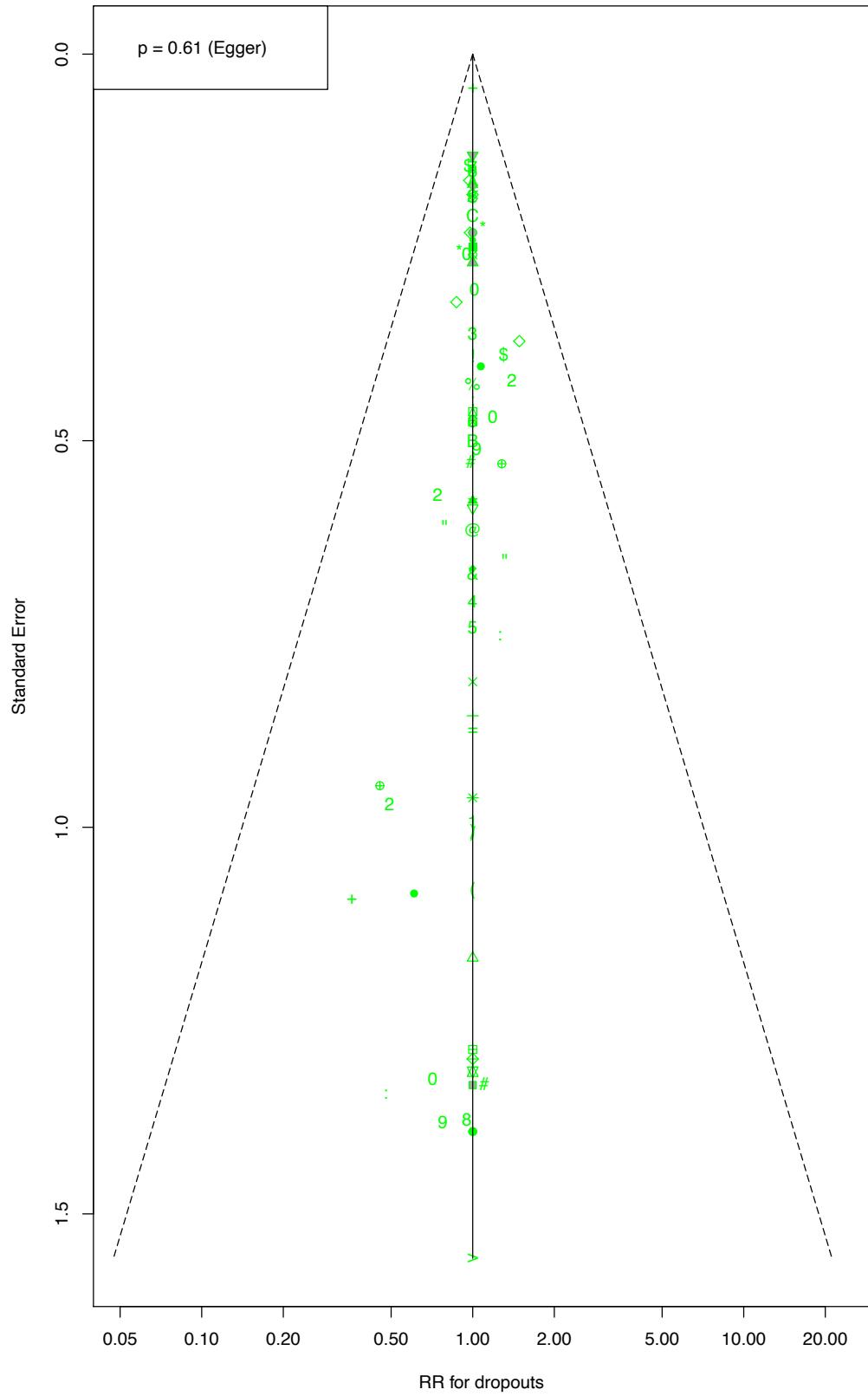
- RR: rate ratio
- SMD: standardized mean difference

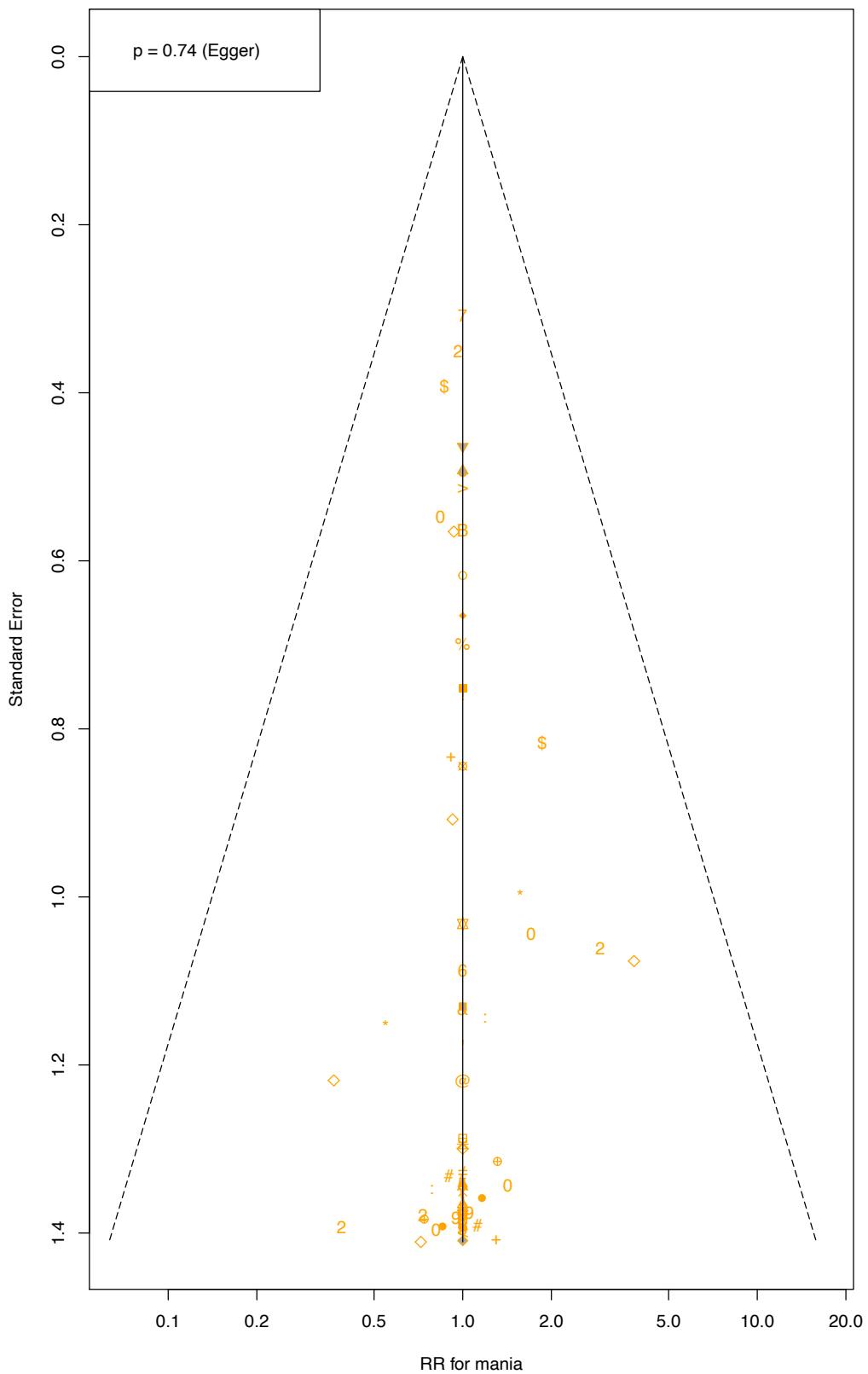
*Appendix 9. Funnel plots and tests of symmetry for publication bias in network meta-analyses.*

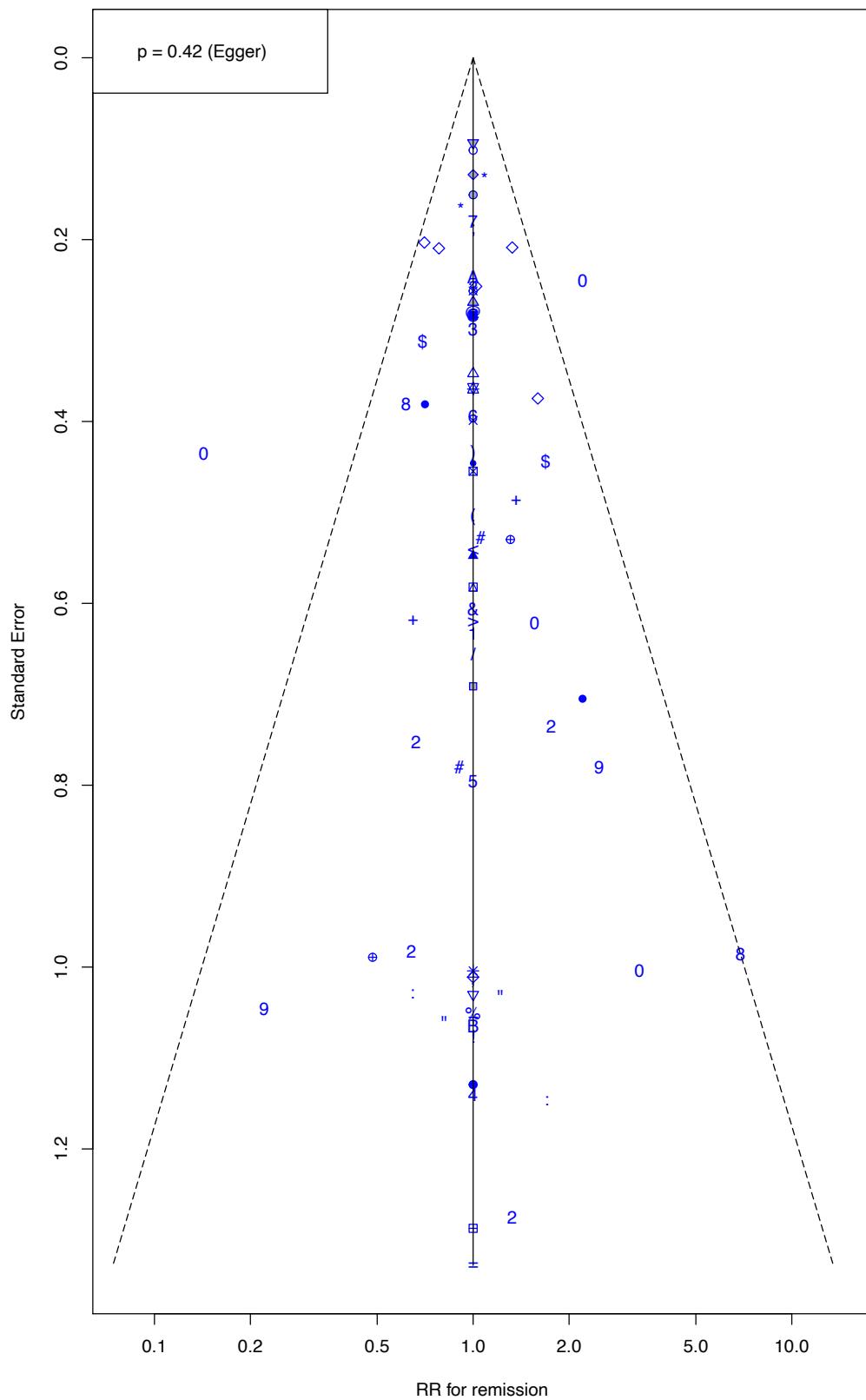


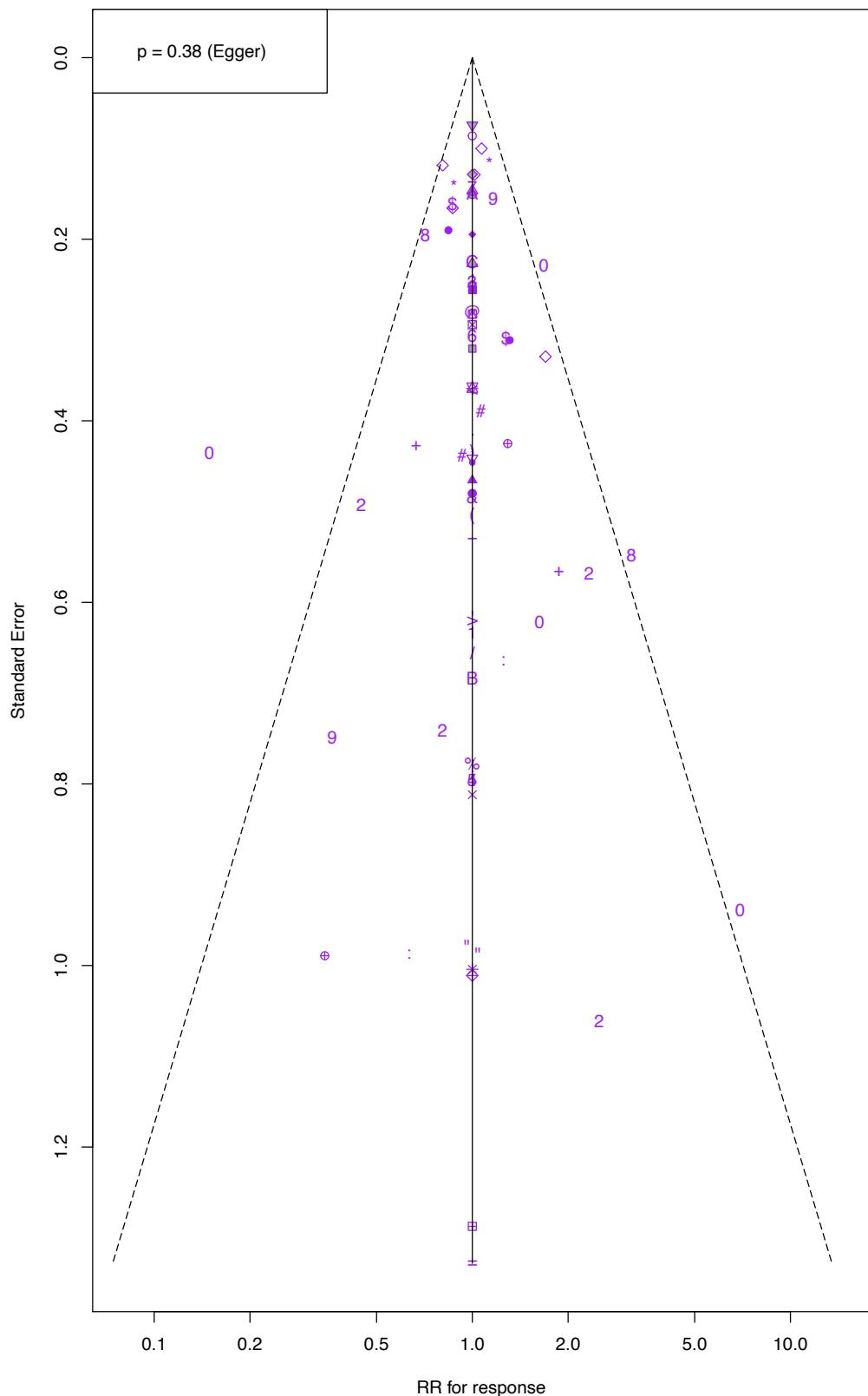










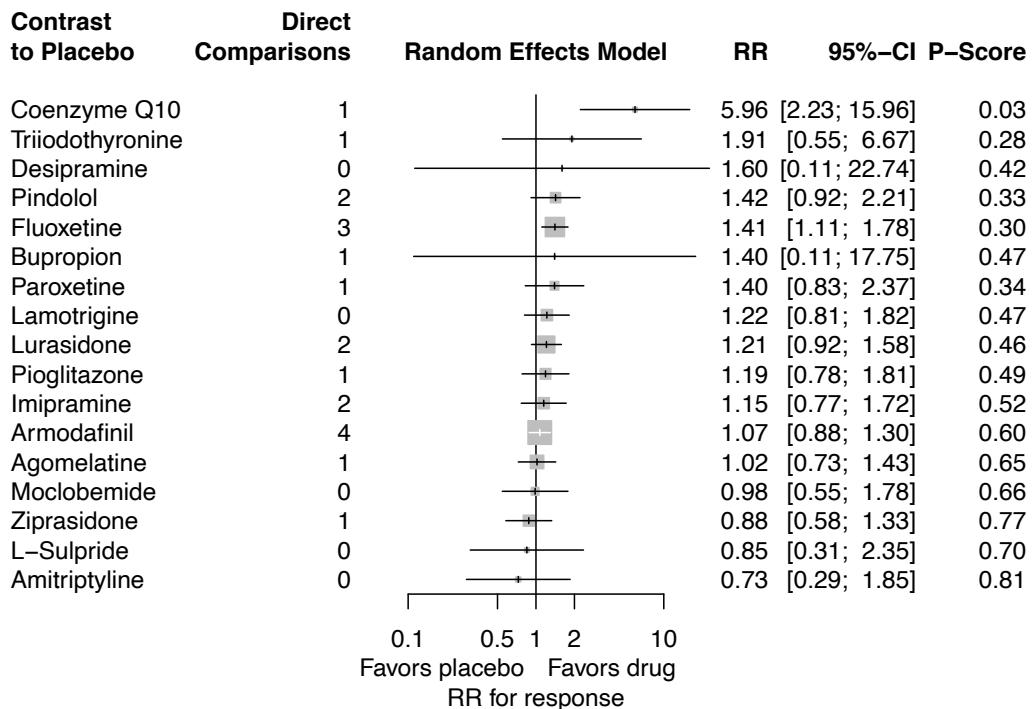


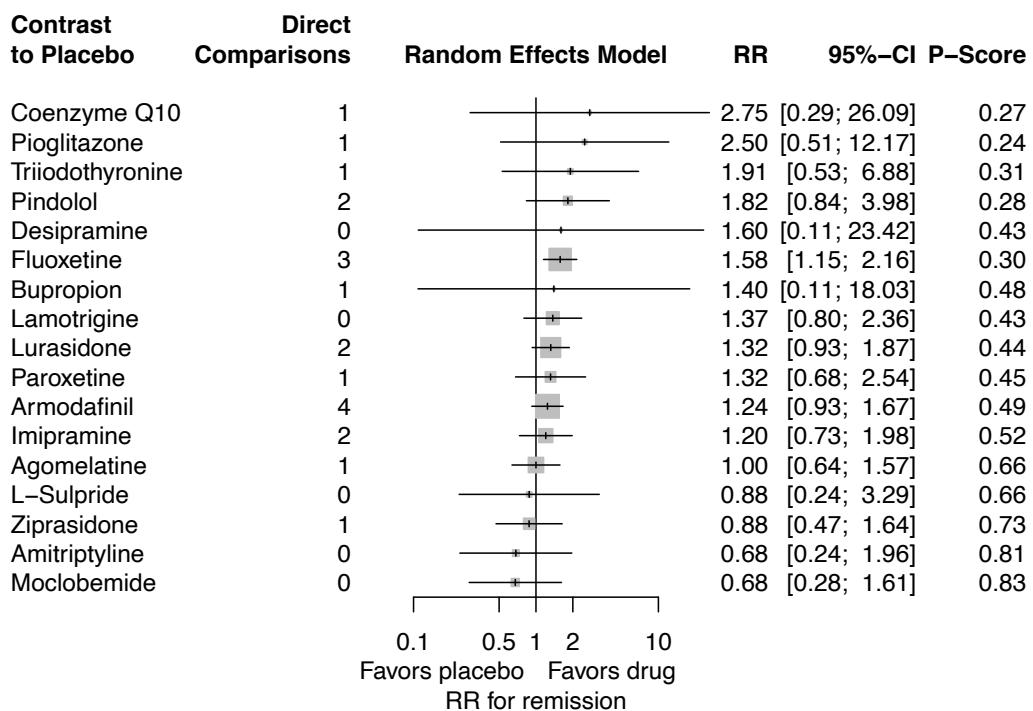
## Appendix 10. Summary of Subgroup Analyses

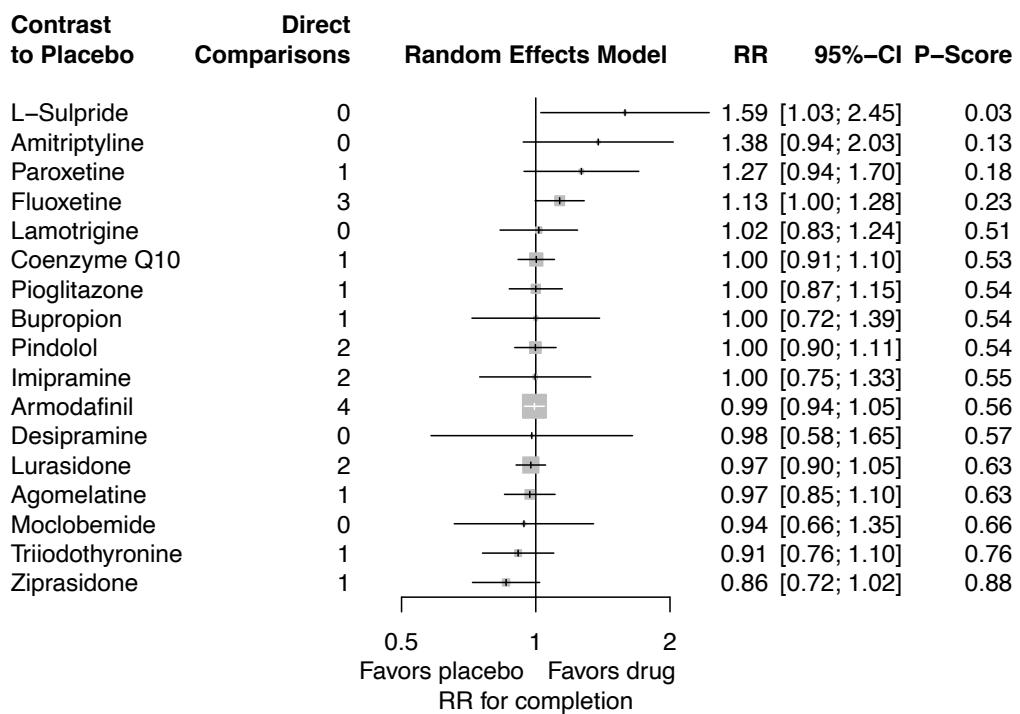
	<b><i>BD-I Only</i></b>	<b><i>BD-II Only</i></b>	<b><i>Multisite</i></b>	<b><i>Non-TR-BD</i></b>	<b><i>N&gt;50</i></b>
<i>Response</i>	Coenzyme Q10	None	Fluoxetine Lamotrigine <b><i>N-acetyl cysteine</i></b>	Coenzyme Q10 Pindolol Fluoxetine	Coenzyme Q10
	Fluoxetine				Aspirin Fluoxetine
<i>Completion of Treatment</i>	Fluoxetine	None	Fluoxetine <b><i>Risperidone</i></b>	Fluoxetine	Fluoxetine <b><i>Risperidone</i></b>
<i>Remission</i>	Fluoxetine	None	Fluoxetine Lamotrigine	Pindolol Fluoxetine	Celecoxib Fluoxetine
<i>Reduction in Depression Severity</i>	Fluoxetine	Pramipexole	Nil	Fluoxetine	Nil
<i>All-cause treatment discontinuation</i>	Fluoxetine	Fluoxetine	Fluoxetine	Fluoxetine	Fluoxetine
<i>Discontinuation due to adverse events</i>	<b><i>Imipramine</i></b>	None	None	<b><i>Combination Nutraceutical Moclobemide Imipramine Quetiapine Extended Release</i></b>	<b><i>Imipramine</i></b>
<i>Treatment-emergent mood switches</i>	None	None	None	None	None

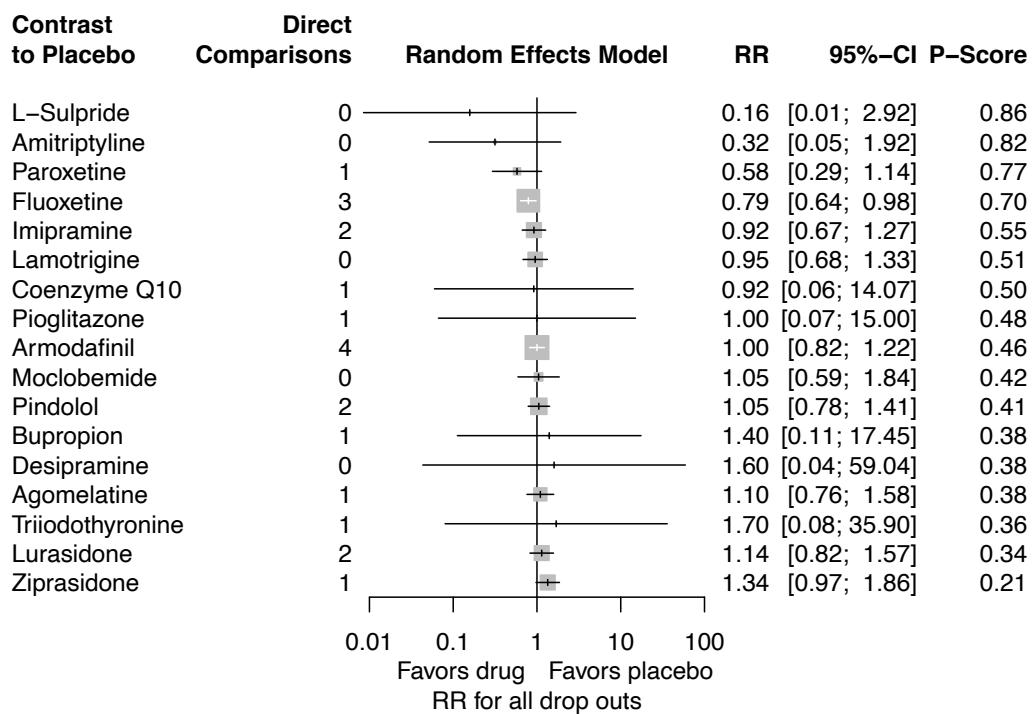
- Black text: agent performed superiorly relative to placebo (e.g., rate ratio of >1 for response, remission)
- Red text: agent performed significantly worse than placebo (e.g., rate ratio of <1 for completion of treatment)
- BD-I, BD-II: Bipolar Disorder, Type I; Bipolar Disorder, Type II
- Non-TR-BD: analyses presented for a restricted sample that excluded patients with treatment-resistant bipolar disorder
- N>50: restricted analysis to studies with at least 50 participants
- Nil: analysis could not be conducted for this outcome measure.

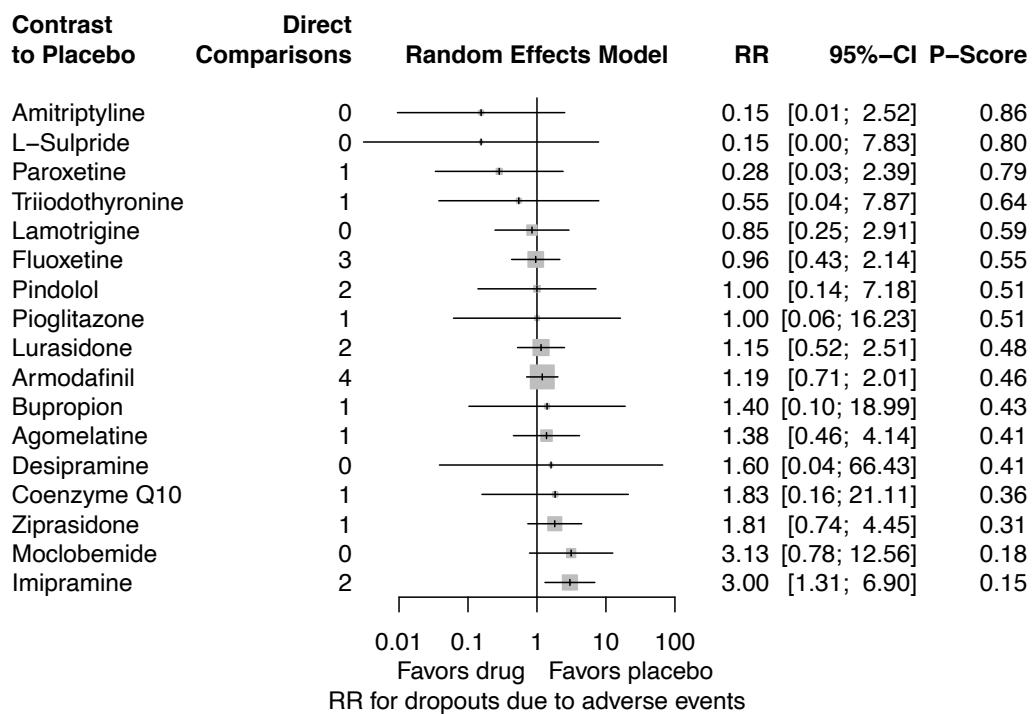
## *Subgroup analyses: BD-I Only*

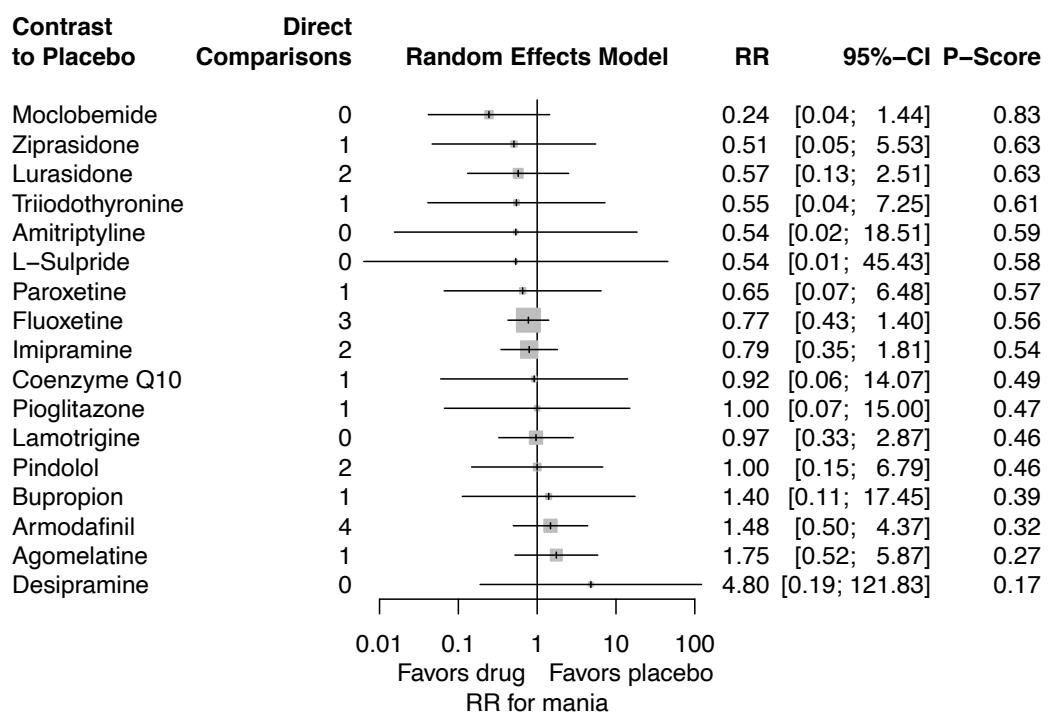




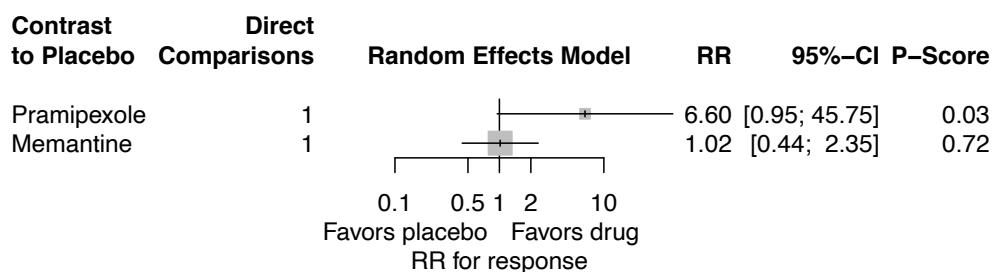


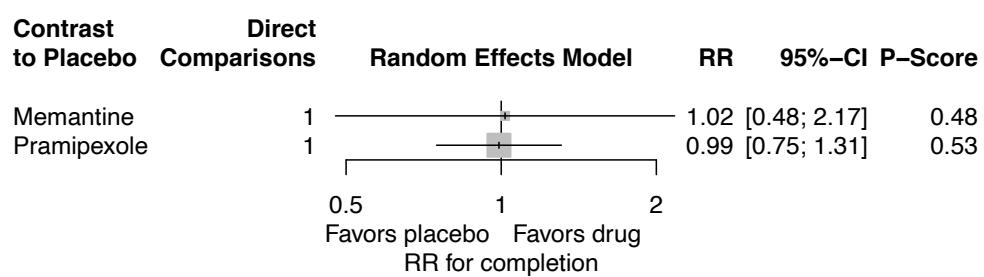


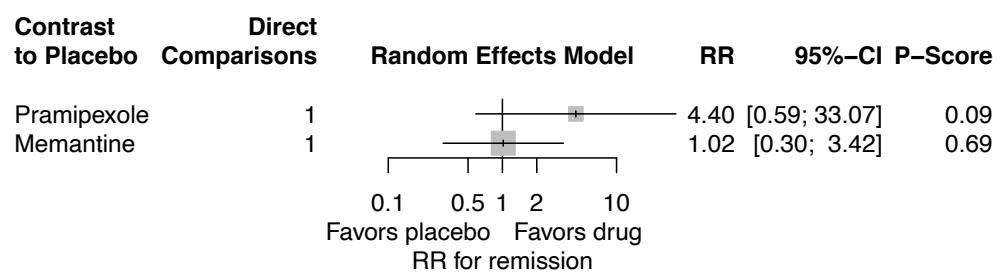


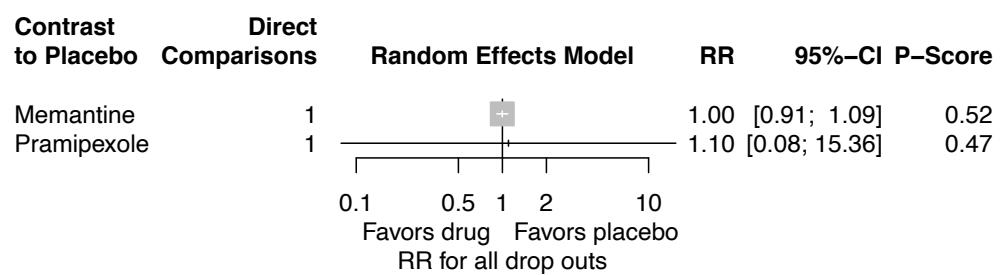


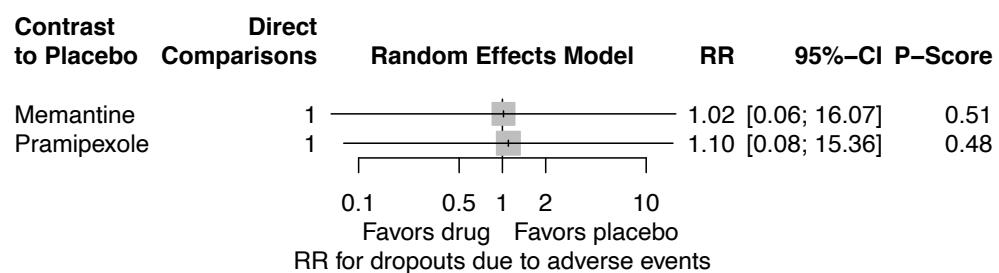
## *Subgroup analyses: BD-II Only*

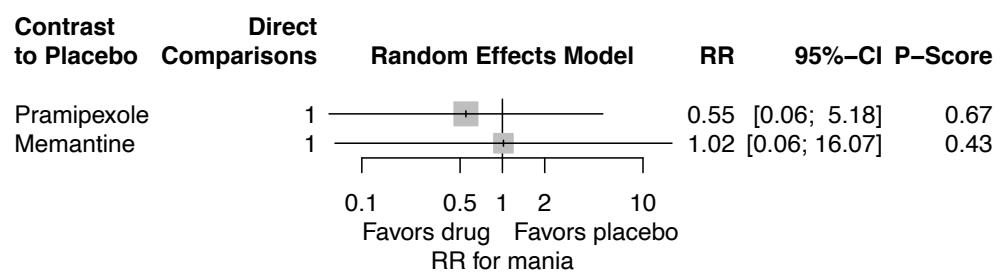


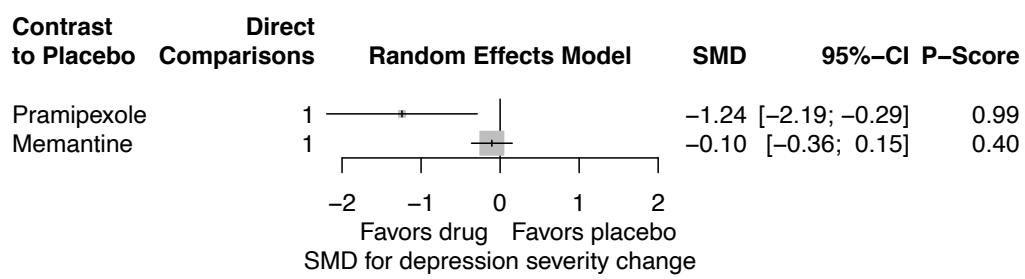




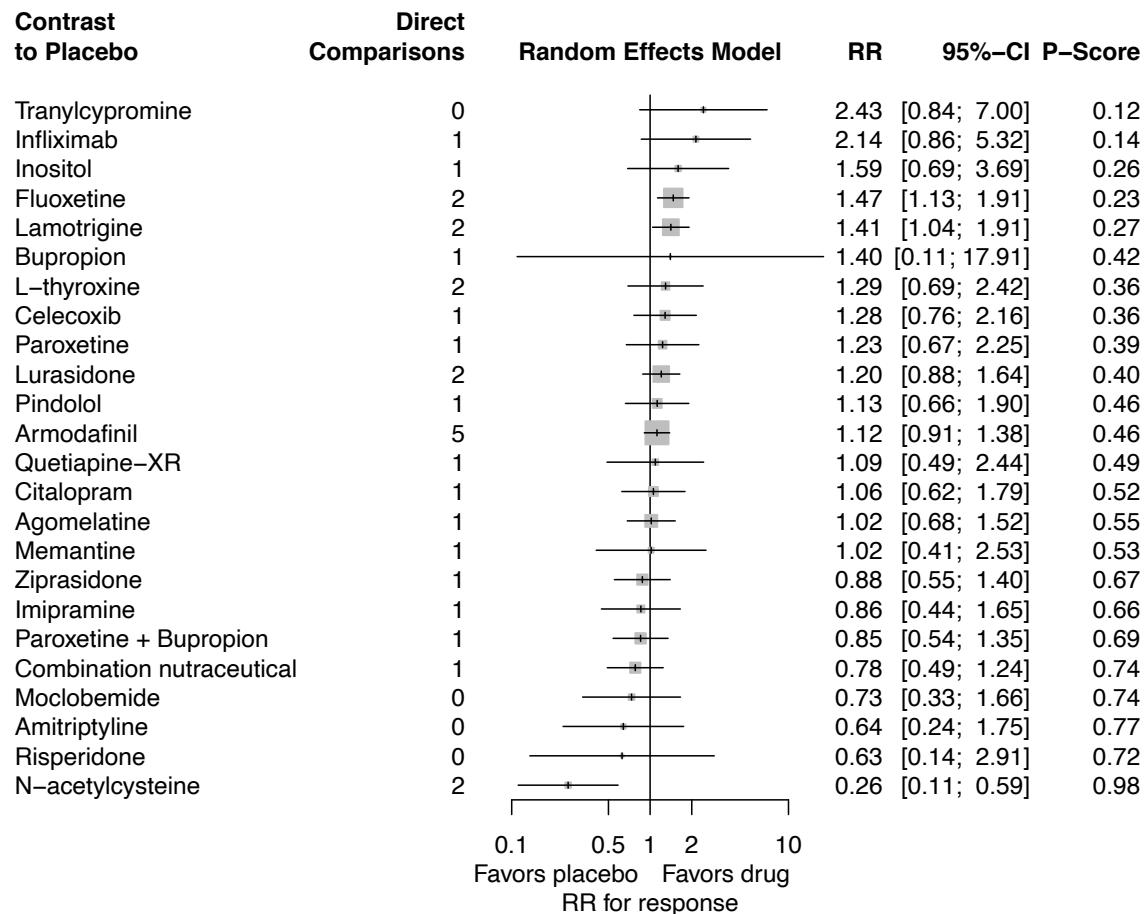


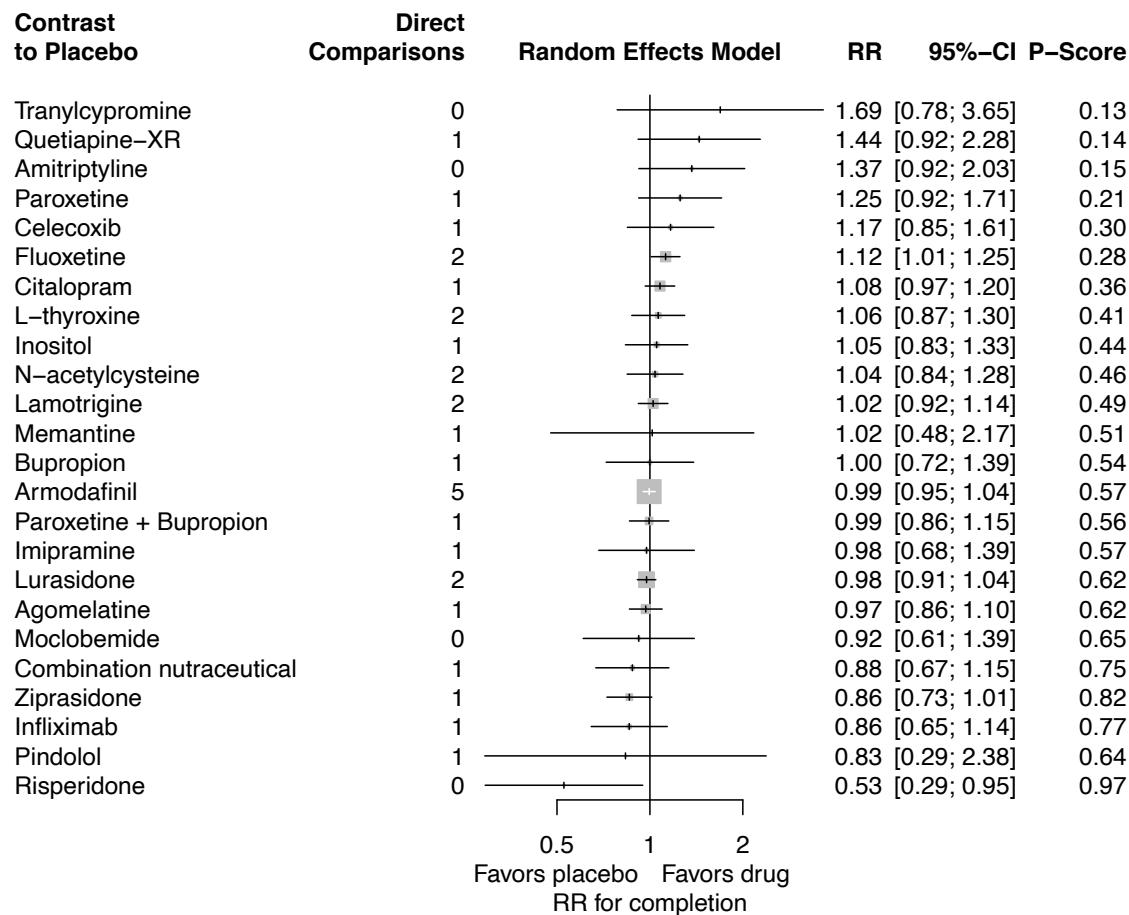


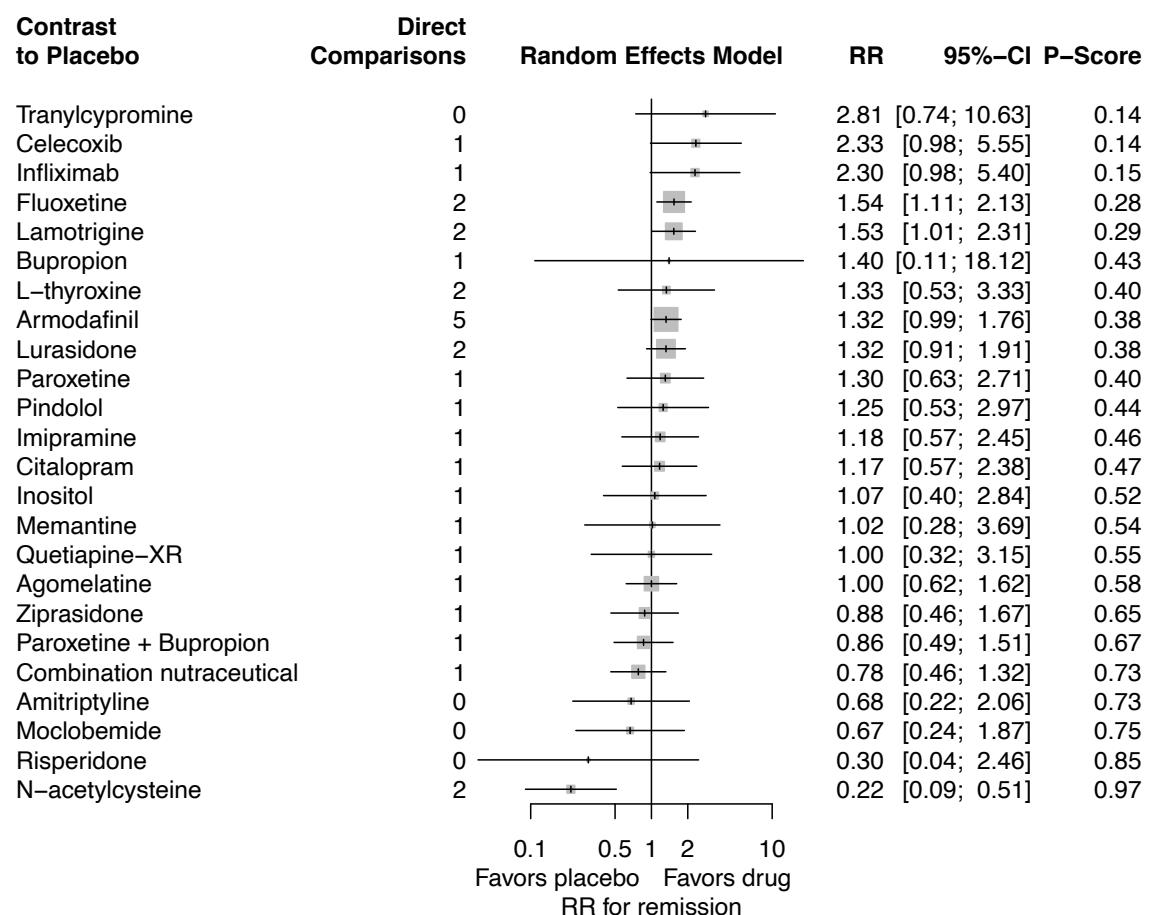


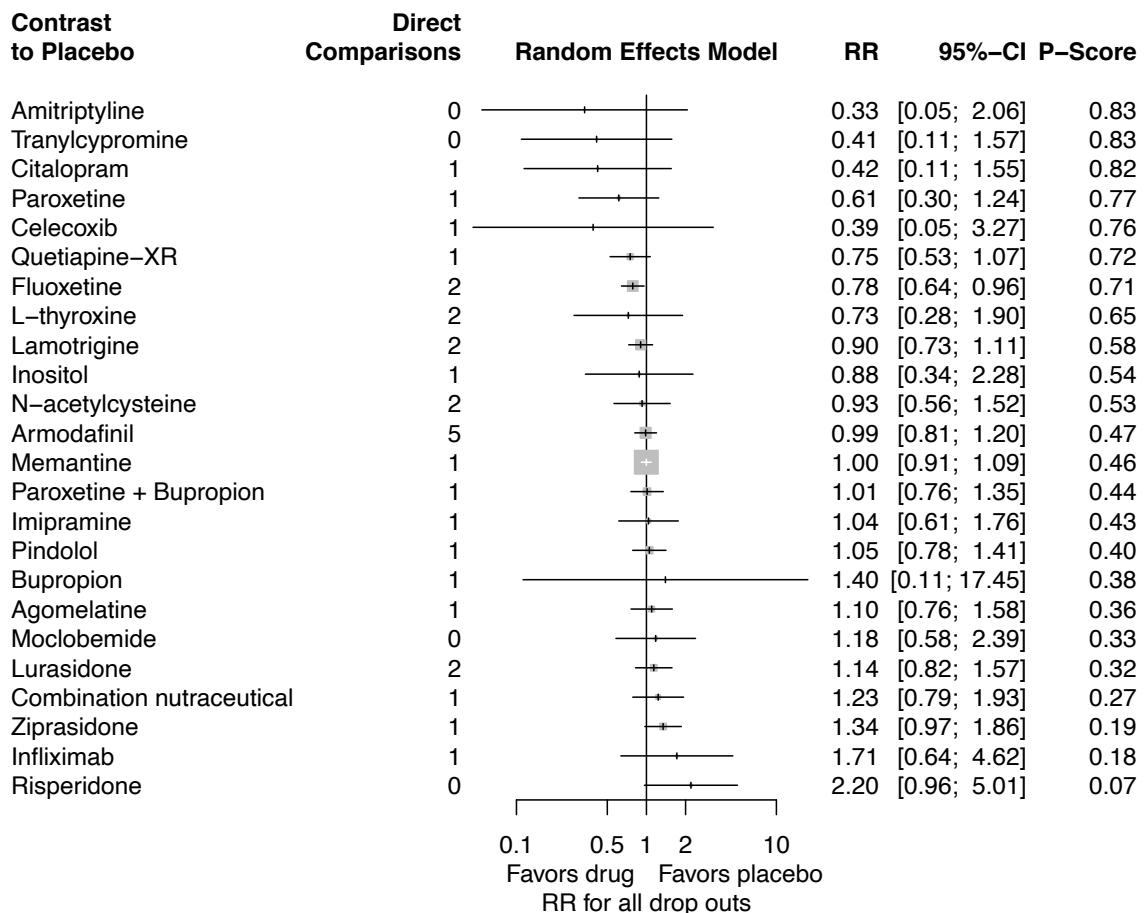


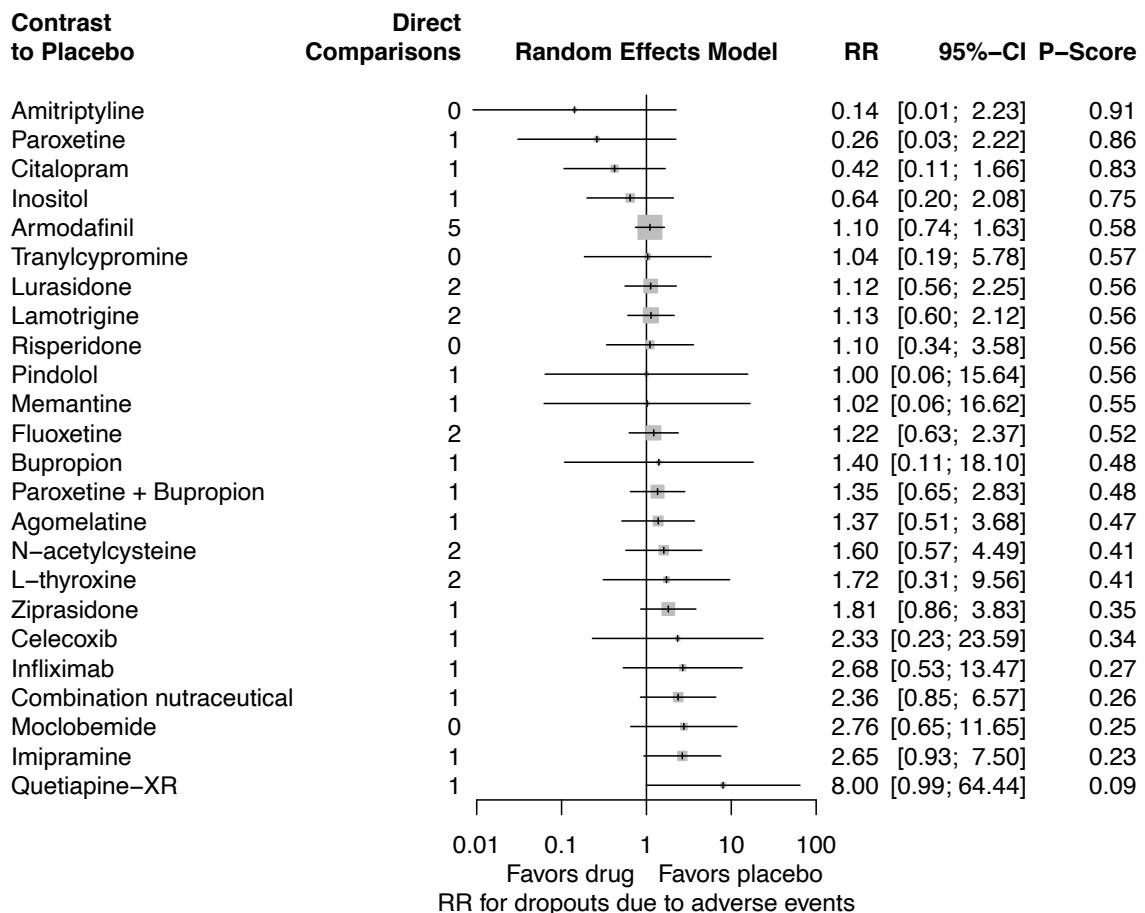
## *Subgroup analyses: Multisite RCTs only*

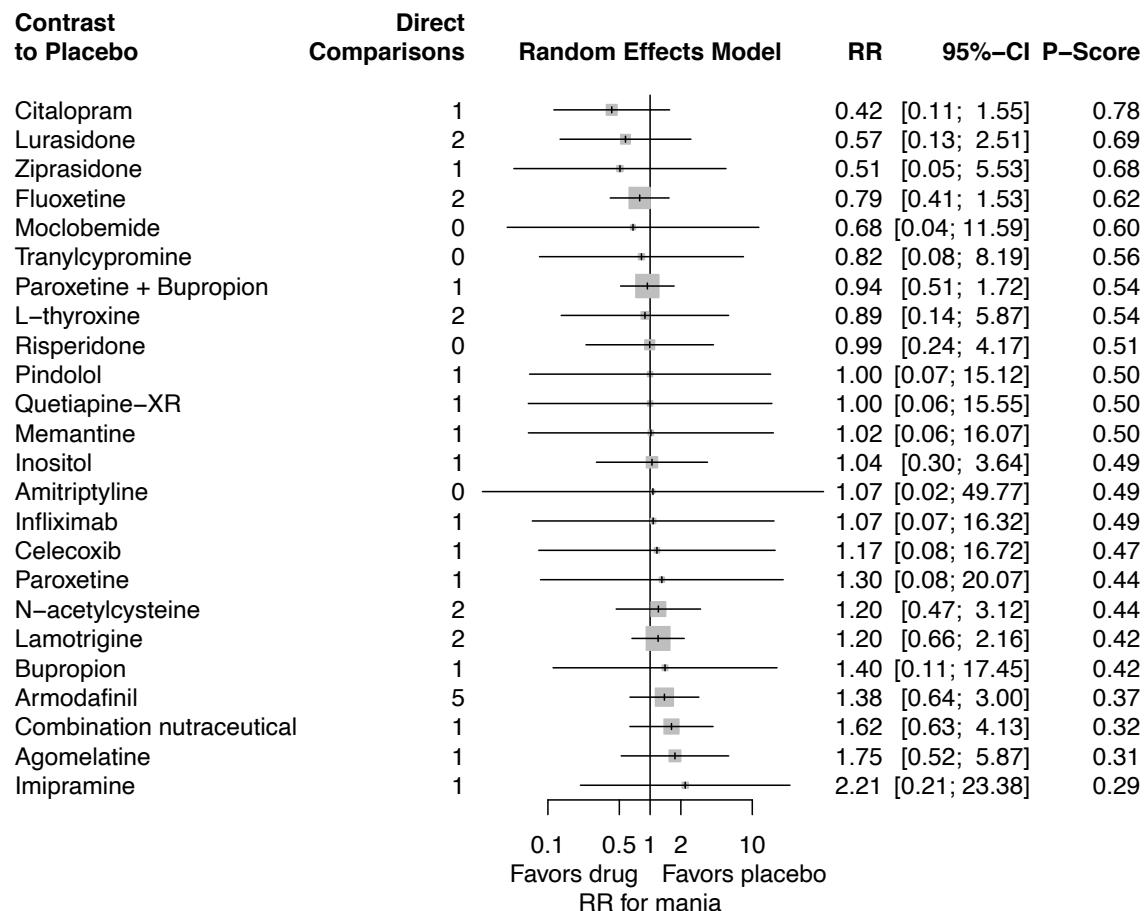












## Subgroup analyses: no treatment-resistant bipolar depression

